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HENRY FORD HOSPITAL MEDICAL BULLETIN

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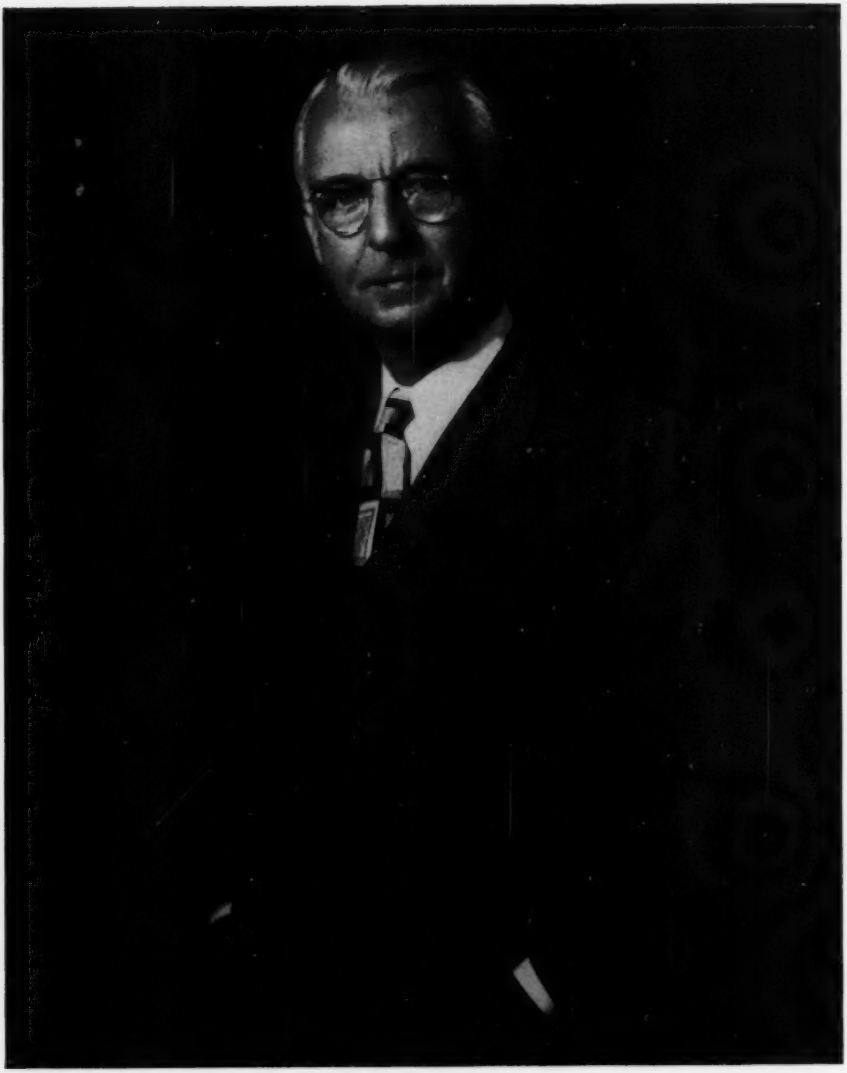

DR. JEAN PAUL PRATT

AFTER OFFICE HOURS
A VISIT WITH DR. JEAN PAUL PRATT

SAM. GORDON BERKOW, M.D.

Ancient Greek drama, to solve its dilemmas, relied on a *deus ex machina.* And now in this country, many persons believe that the national economy can be rescued only by a god out of a machine. Perhaps it is not too whimsical to say of this god that Detroit is his Olympus, or his Mecca, and Henry Ford was his prophet.

When I arrived for this visit, Detroit was in the slough of the 1958 recession. Taxi drivers and other *cognoscenti* discoursed freely on unemployment, which they claimed was the highest in the nation. It was evident, too, that the city, and its troubles, had grown up around Henry Ford Hospital; but the sprawling hospital buildings were being repaired, remodeled, and enlarged, and the clinic building, a 17-story skyscraper which towers above them, was a beehive of activity.

In the clinic building, the numerous offices are functional, almost uniform in size and appointments. But through the open door of Dr. Pratt's office one sees hanging on the wall, where it must catch the eye of the passerby, a framed picture of two beautiful women photographed against a tapestry background. These are, the receptionist whispers, Dr. Pratt's wife and daughter.

Dr. Pratt is slender, and only a full head of whitening hair betrays his age.

"Henry Ford Hospital is a unique institution," he said when we shook hands and sat down to talk. "It was started in 1911, but actual construction came later and it was incorporated as The Detroit City General Hospital, a nonprofit institution, in October, 1915. It was controlled by a Board of Directors, one of whom was Henry Ford. Now, Henry Ford never liked Boards, and at one of the Board meetings there was a dispute as to policies, so Mr. Ford said that he would either buy out the other interests or sell his. It ended by his buying out the others, and it became the Henry Ford Hospital'.

Later, the Assistant Director of the Hospital told me that Henry Ford Hospital started out in a small way, with only 3 floors. The first floor had administrative offices and the upper 2 floors were primarily for patients. Altogether there were 49 beds. "Present capacity is somewhat in excess of 850 beds," he said. "We are now in the process of adding approximately 200 beds, so that by Christmas of next year our bed capacity will be in the neighborhood of 1050."

Dr. Pratt came to the Henry Ford Hospital in 1917. "This is the way it came about," he said. "In 1916 Dr. Sladen was the first Chief of the Medical Service, and he brought Dr. McClure to Detroit to become Chief of the Surgical Service. Dr. McClure soon realized that he needed an associate, and because I had been associated with him as a resident in surgery at Johns Hopkins Hospital, we were well acquainted. He invited me to come to Henry Ford Hospital.

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"When I received Dr. McClure's invitation I had established a profitable practice in San Francisco for 4 years and I thought, Why should I leave to go to an institution? But then I thought this might be an opportunity that I could not afford to miss. After some correspondence, I came to see Henry Ford Hospital. I was so impressed that I was glad to give up the better remuneration of a private practice for what this institution offered me."

BACKGROUND

"This is my background: I got my medical degree from Johns Hopkins in 1910. Then I had a surgical internship and residency under Dr. Halsted. Among other things, I was Dr. Halsted's anesthetist for 2 years, which was a very interesting and valuable experience. It gave me an understanding of anesthesia, which proved useful in all of my surgical and gynecologic practice. It would be helpful if every surgeon had a good training in anesthesia. Halsted was a pioneer: he wanted to make surgery a science. Science was everything. Consequently, or because it was his nature, he was very scientific, methodical, and analytic. Dr. Finney was also an excellent surgeon and teacher, but his patients also considered him as their friend and advisor."

After his internship and 2 years' residency in surgery at Johns Hopkins, Dr. Pratt decided that it was time to go into practice. San Francisco seemed an ideal place to live, so he decided to go there. His only contact in San Francisco was Howard Naffziger, who had studied 1 year with Harvey Cushing at Johns Hopkins. During that time Dr. Pratt got to know him very well. "Dr. Naffziger was a well-known and wonderful neurosurgeon," Dr. Pratt said. "He became president of the American College of Surgeons."

Of this association Dr. Pratt speaks with warmth. "I shared an office with Howard for 4 years. We had a common waiting room and laboratory, and each of us had his own office. I became instructor in surgery at the University of California. Up to that time there was no course in surgical pathology at the University of California. So I was given a laboratory and a technician, and I accumulated the material for a course in surgical pathology."

Soon after he came to San Francisco, Dr. Pratt discovered that, outside an institution like Johns Hopkins, a general surgeon had to do gynecologic surgery. When he was offered the opportunity to associate himself with doctors who were doing good gynecology, and particularly with Harold Brunn, he accepted gladly.

HENRY FORD HOSPITAL

Dr. Pratt came to Henry Ford Hospital to do general surgery as assistant surgeon-in-chief. "Why?" He answeerd, "Because I saw an opportunity for clinical research. I could accumulate groups of patients to study medical problems intensively, for there was teamwork here, so that when any man was interested in a particular problem the others in the hospital tried to see to it that all such cases came to his attention. There is reason to be very grateful for the decision to come to the Henry Ford Hospital because many of my hopes and ambitions were realized: for example, studies of carcinoma of the rectosigmoid, search for human ova, studies on benign breast lesions.

"This was, as I said, a unique institution — in this part of the country at least. Mr. Ford, who was personally interested in the hospital and came here frequently, believed that going to a doctor should be like going to a department store where one could shop and get the best for the money paid. He believed in building the self-respect and pride of the working people by giving them the best medical service obtainable for what they could afford to pay."

Dr. Pratt acknowledged that in the beginning the physicians in Detroit were fearful that the Henry Ford Hospital would be serious competition to private practice. "It has kept down excessive fees, but at the same time it has done a great deal for the local medical community. It helped to educate the public to appreciate the value of a thorough examination and to expect to pay their physicians for time spent."

There was a time when Mr. Ford would have liked to sell drugs to the patient at cost plus a small fee, but the business office found that the local druggists insisted that Henry Ford Hospital charge for medicines at the going rate in this community. "There was a good deal of pressure exerted, so it was not possible to do anything else.

"Still," Dr. Pratt insisted, "we — the medical staff — were allowed to proceed much as we thought a hospital should be run. Mr. Ford was a genius and had some marvelous ideas, about nutrition for example. He wanted the doctors to set up a laboratory and test his theories. There were a few things like that, but really there was very little interference and we were allowed to practice medicine as we doctors thought medicine should be practiced.

"There is further evidence of the Ford family's interest in the Hospital. In the 1920s Henry Ford and his wife established the Clara B. Ford School of Nursing here. They were tremendously interested in training registered nurses." Now there are approximately 300 nurses in the school.

"In the beginning," Dr. Pratt said, "the surgical staff was limited to 3 of us besides the interns. Each one did general surgery, but included what later became a separate specialty. I was covering gynecology, general surgery, and orthopedics. Then an orthopedist came and I was relieved of this part of the work. That situation prevailed as late as 1926.

"At that time a very nice relationship existed between gynecology and obstetrics. Ed Plass was here doing obstetrics and I was doing gynecology, and very happy about it. Then Dr. Plass developed tuberculosis and could not carry on the necessary night work, so he resigned from the hospital. Dr. Plass's assistant, Dr. Siddall, took his place for a year, and then he decided to go into private practice. So, having lost two heads of the department in 1 year, I was prevailed upon to take over obstetrics, thinking I could just supervise it and do only gynecology. But I found it difficult to be head of a department of obstetrics without doing some obstetrics."

TRAINING

The value of a good surgical training as a background for obstetrics is emphatically asserted by Dr. Pratt, on the basis of his own experience. "Some of the medical and chemical problems of obstetrics change a great deal from time to time," he said.

"These necessitate careful study constantly, to know what is the best practice. On the other hand, many of the more difficult problems, which require immediate attention, are really surgical problems, in which surgical experience and knowledge of surgical principles is immensely valuable."

Speaking of his personal background, Dr. Pratt said: "My father was a school teacher and a farmer. I was born on a farm in northern Ohio, in the shadow of Oberlin College. I liked farming, and I feel that I learned a great deal from my experience on the farm. To cite one specific example: During my late teens I became interested in the feeding of hogs, and I recall weighing very carefully a group of hogs and then measuring their feed, trying to get them on a balanced ration. I observed that the hogs that had just enough food so that they ate it all and then left the empty trough to lie down and just build fat would gain as much as 2 pounds per hog per day. When I gave them more than they could consume at once they gained very slowly.

"Also the illnesses of animals were a challenge which stimulated an interest in human problems. The possibility of studying medicine was vaguely attractive. The family doctor, who traveled in a one-horse cart through mud and rain, repeatedly advised me never to be a doctor. Little did he realize the future with the development of the automobile.

"I started in the Agricultural College but after 3 months at Ohio State I transferred to the liberal arts course for premedical training. In 1906 I received a B.A. degree there, having majored in biologic studies, particularly zoology, comparative anatomy, and embryology. In the latter subjects Prof. Landacre was an outstanding teacher, one of the best I have ever known. It was through his influence that I chose to go to Johns Hopkins for my medical course."

ENDOCRINOLOGY

Dr. Pratt has long been a leader in the field of gynecologic endocrinology. His collaboration with Edgar Allen was particularly fruitful. "Our association came about in this way," Dr. Pratt said. "In September, 1923 I saw the brief note of Allen and Doisy in the *journal* of the A.M.A., about the follicular hormone they had obtained and purified. I was fascinated. So I asked Edgar Allen to come to a meeting at this hospital and tell us about his investigations. He came, and that was my first acquaintance with him. I asked some questions, to which he replied: 'I don't know the answers, but why don't we find out?' That started a very pleasant relationship. I sent a great deal of material to Edgar Allen and we corresponded, and then for one summer he came and stayed at my home and we worked in the Henry Ford Hospital laboratory. Our particular project was to look for an ovum in the uterine tube."

The inspiration for that study came from Carl Hartman. "On a visit to Carnegie Institute I was chatting with Dr. Hartman in his laboratory when he sort of flipped an opossum egg through the salt solution and said, 'There! Why don't you find a human egg?' I said, 'I will.' So I inquired how he had obtained the opossum ova, and then I got in touch with Allen and we set up a joint study to find the ovum after it has left the ovary, by washing out the uterine tubes. Allen also worked with

Newell and Bland in St. Louis. We had two groups working on this problem. In a group of women who needed surgery, operations were scheduled for the time when we would be most likely to find the ovum; that is, after a recent ovulation. We studied the corpus luteum, ovulation, the follicles. When we discovered the ovum in the tube it was a happy occasion, the fulfillment of a dream. I reported this finding in a paper read at the A.M.A. meeting in Portland and it was published in the *Journal* in 1925."

Absorption in endocrine aspects of gynecology continued. In 1933 Dr. Pratt became president of the Association for the Study of the Internal Secretions. "For several years after that I was on the Board," he said. "I had a very pleasant association with the men who were doing endocrine studies at that time, and I hope I had some influence in keeping the Association on a sound level. It is no secret that there were many attempts to commercialize that organization and get it away from its sound scientific basis." As president and a member of the Board he resisted "the tendency for the laboratory men to usurp the field." His efforts to increase the influence of the clinicians, "not to subdue the laboratory but to encourage the clinical side," contributed to the decision of the Society to publish a clinical journal as well as a laboratory journal. "I maintain my interest in endocrinology," Dr. Pratt said. "It is a very important part of gynecology. I am grateful for having had the opportunity to live in the early days when the sex hormones were isolated and identified. Following the discoveries as they are made gives one a sound perspective."

Dr. Pratt wrote the chapter on pituitary-ovarian and placental relationship in Tice's *System of Medicine*. He also contributed the chapter on endometriosis in Sajou's *Encyclopedia of Medicine*. "My interest is clinical, but I have tried to follow the experimental work carefully," he said.

UTERINE CANCER

Experience with radium, x-ray, and surgery in the treatment of uterine cancer, both endometrial and cervical, led Dr. Pratt to the "logical conclusion" that one adds to the total possibility of a cure by using all three, if possible, or by some combination. "Sometimes we use radium and surgery; often deep x-ray therapy is added," he said.

"Operating after irradiation, we have had an opportunity to observe the effects of irradiation. In the early days there was no precedent to tell us exactly when to operate after radiation. In consequence preoperative radiation was sometimes condemned because it was thought that it increased bleeding. By following the results clinically, I found that 4 to 8 weeks after the application of radium to the cervix the edema had subsided. We found that radiation before operation actually improved the facility of the operation. It has been our policy to wait 4 to 6 weeks after radiation to do a hysterectomy.

"A very interesting patient taught me that radiation is useful for carcinoma of the fundus. She was referred because she was thought to have carcinoma of the fundus. The local surgeon had operated. He wrote that she was so full of adhesions that it would be impossible to do a laparotomy. What could we do for her? It would have been questionable to have even tried to do an operation after such an introduction.

The patient was given radium into the uterine cavity and then observed again in a year. At this time the uterus was curetted and no carcinoma was obtained. Nevertheless, she was given a second course of radium. That patient was followed for several years and never had any recurrence of the growth. So we continued using radium before operation in carcinoma of the fundus, with a great deal of satisfaction. Also in carcinoma of the cervix we combine radiation and surgery. Now that cobalt is available, it adds another interesting modality and is very useful. If the uterus is large I am inclined to use deep x-ray therapy to shrink the cavity. With the early applicators it was difficult to reach all parts of the uterine cavity with radium, and some of the failures I believe were due to inability to apply the radium to the carcinoma rather than that the carcinoma was not sensitive to radiation. Some combination of radiation and surgery has been selected according to each individual with satisfactory results."

RECTOSIGMOID CANCER

Study of a group of 100 patients with rectosigmoid carcinoma "worked out very satisfactorily." That *arbeit* began in the early 1920s, when Dr. Pratt was still doing general surgery. "A woman with rectosigmoid carcinoma was referred to us. I told her she must have a colostomy. She said she knew what she had, she knew the consequences, and she would not have a colostomy. Well, I just couldn't let her go. So I decided to do something other than a colostomy. What I did was a radical abdominal dissection of bowel, largely on a bisis of the Miles operation, then pulled this bowel through an incision below the coccyx. The bowl was resected, anastomosed, and the continuity of the bowel preserved. This woman was symptom-free for 19 years, and then developed an extensive carcinoma of the same type as the original tumor. In the entire series of 100 — which included 1 patient who had half her liver destroyed by carcinoma, and others with metastasis — the 5-year salvage was 65 per cent, which was very good at that time."

Dr. Pratt mentioned an interesting "sidelight" to this study. The surgical resident, Dr. Altemeier (now Professor of Surgery at the University of Cincinnati), observed that the patients operated upon for carcinoma of the rectosigmoid never had peritonitis. All these patients, like those with uterine cancer, had been subjected to preoperative radiation. So Dr. Altemeier experimented with rabbits, giving some deep x-ray and then injecting the same lethal dose of bacteria into the peritoneal cavities of all the rabbits. He found that a dose that killed an untreated rabbit in a few days was not harmful to an irradiated rabbit, and that the optimum protection was at 4 to 6 weeks. "So it was demonstrated that, without our knowing it, we were also protecting our patients from infection by preoperative x-ray therapy, and also confirmed that 4 to 6 weeks is an optimum time."

PSYCHOSOMATIC MEDICINE

A pioneer in psychosomatic gyneoclogy, Dr. Pratt tells an interesting anecdote about the first paper on this subject which he submitted for publication. He says: "I had given thought to this subject from the early 1920s. In 1929, at the Philadelphia Obstetric and Gynecologic Socitey, I read a paper entitled *The Emotional Problems of Obstetrics and Gynecology*. It was well received, and they sent the manuscript

to the *American Journal of Obstetrics and Gynecology*. Dr. Kosmak returned the paper to me, saying that he was interested personally, but felt that the material was not suitable for the *Journal*. Later, after George Kosmak had himself written extensively on the same subject, I chided about that paper. "Well,' he said, 'send it back.' 'No,' I said, 'you turned it down and it's on the shelf, where it will stay.' I tell you this story to show that psychosomatic gynecology just wasn't accepted at that time."

Even now that it is an important part of the training of the resident in obstetrics and gynecology, some doctors, he finds, have diffculty in understanding psychosomatic problems. "Often a resident will come to me and say, 'Dr. Pratt, I know the patient has a psychosomatic problem, but I don't know what to do.' Other gynecologists, capable of evaluating such a problem, feel that if they recognize the problem, they must send the patient to a psychiatrist. My own feeling is that each specialty in medicine should be able to handle the bulk of its own psychosomatic problems. That's the art of medicine."

TERMINAL CARE

Presently Jean Paul Pratt is concerned with the problems of terminal care. "Have you had an experience like this?" he asks. "You are making rounds with a doctor, and he says, 'I hope that woman in number 23 will be asleep so I don't have to talk to her. She is dying of cancer.' Well, such a doctor would rather avoid the issue he should face. I say of the patient who has come to the condition of terminal care, that if she ever needed a doctor she needs one then."

He spoke on this subject more recently at a Pan-Pacific conference in Hawaii. He said: "Death is inevitable. Instant death is for the fortunate few . . . Medical attention has been, and still is, focused upon diagnosis and treatment. Too little attention has been given to the problems that occur when all attempts to cure have failed." He then listed the various problems (such as, what to tell the patient) and considered each in detail.

EMBOLISM

At this point in the visit one naturally expects Dr. Pratt to view medical problems from a broad and humanitarian standpoint. This expectation is agreeably confirmed by his discussion of embolism. "I am very much disturbed by the sudden death of patients from embolism," he states. "Embolism has been a serious problem over the years. Although there has been great improvement in the control of one factor, infection, since the introduction of sulfa drugs and antibiotics, there has been no substantial improvement in our handling of the second important factor, stasis of blood entering the blood vessels. It occurred to me that a good deal could be done to prevent stasis by careful preoperative medication, anesthesia, and postoperative care. I like to prepare a patient psychologically for her operation, so that she will need very little sedation. If I cannot see her myself, I arrange for a resident to see her on the night before operation, and if she has any questions that have not been answered previously, they are answered now, so that she goes to the operation with a free mind. The medication before operation is light, preferably Seconal, because it acts quickly and wears off quickly. The anesthesia of choice is ethylene gas or a little ether. Spinal anesthesia is generally avoided because it causes profound stasis of blood for a long

period of time. Morphine is also avoided because it causes stasis of blood in the mesenteric vessels. Postoperative medication is minimal in my practice. I want the patient to be a little restless and to roll in bed. This prevents stasis. Since 1939, when I instituted this regimen, I have had only one death from embolism, and I believe that much of this change from earlier days can be credited to the avoidance of stasis as well as to the new drugs for treatment of infection. Early ambulation? It has undoubtedly been beneficial in calling attention to the necessity of avoiding stasis, but it seems to me that getting the patient up the next day, or even a few hours after operation, is locking the stable after the horse is stolen."

TRAUMATIC MASTITIS

What else has particularly interested Dr. Pratt? "Traumatic mastitis," he answered promptly. "Cancer of the breast was one of Dr. Halsted's major interests when I was on his service as intern-resident, and for that reason the problems of the breast diseases and breast surgery have continued to intrigue me. I have continued to use Halsted's radical operation for cancer of the breast. With experience in surgery, gynecology, and obstetrics, I have had an opportunity to see a great many benign lesions, some of which appeared as definite lumps. One type which has particularly attracted my attention I have called traumatic mastitis. The first one I saw was diagnosed as benign tumor, and operation was advised. The patient did not follow the advise; she came back to the clinic a month later and there was no lump.

"Over the years there have been a large group of such patients. They have a definite lump in the breast and sometimes the lumps are multiple, and usually tender. They are definitely related to injury: not to a single injury but repeated small injuries. In earlier days one of the common types of injury was from whalebone stays in corsets. The present day trauma is largely from a type of brassiere which, day after day, exerts a point or line of pressure. Many of these traumatic mastitis lumps have been seen here. We advise the patient to return for observation, and with this course she is saved from unnecessary surgery, for when the trauma is removed the lump disappears. And when this occurs one can be sure the lump was not malignant. Of course, one assumes a great responsibility in not operating when a lump is found. The condition requires a great deal of further study. I read a paper on inflammations of the nonlactating breast at a meeting of the American Gynecologic Society. It was published in the *American Journal of Obstetrics and Gynecology*. The particular condition I wanted to emphasize in this paper was traumatic mastitis."

SEMIRETIREMENT

In 1952 Jean Paul Pratt retired from active direction of the Department of Gynecology and Obstetrics at Henry Ford Hospital. His hours, and remuneration, were reduced. He has his own office, examining rooms, nurses, and secretary and conducts "a consulting private practice" for 10 months of the year. He lives in a large and lovely home situated on the grounds of the Detroit Golf Club. He calls it "an oasis in the city." It is just 15 minutes' ride from the hospital.

In his leisure time he cultivates the roses "over there just beyond the birch trees." Golf? "I played golf until the war (World War II) began, and then the shortage of doctors made it difficult to play. You started to play and reached the farthest hole

from the clubhouse, and then you received a call from the hospital. Soon no one wanted to start a twosome or foursome with you. So I quit golf and went into gardening, and that's the way it has been ever since."

February and March the Pratts spend in Florida. Here, he says, he gets a good rest; but part of the time is spent in boating, deepsea fishing, and gardening. "The problems are so different and the work is so rewarding for the little time spent."

The rest of Dr. Pratt's time is taken up by medical, chiefly gynecologic, meetings in this country and abroad. Last year he lectured in Hawaii, and several years ago in Mexico.

His wife, the lovely Mimi Uline Pratt, provided the following information: "In his 40 years at Henry Ford Hospital, there have been many men who have benefited by his training. These are 'his boys.' He has never forgotten any of them and I am sure that they have not forgotten him. They are scattered all over the world. Rarely a week goes by that he does not get a long distance call at home from one of them with a problem that they want Jean to help solve. When I call him and say, 'It is one of the boys,' his face beams. He is so glad that he can be of some service to them. I have had so many requests for his photograph from his 'boys' when they leave, that I have had a stock made up. I have sent out over 50 to the 'boys' who want to hang on their office wall. One of them said, 'I want it there so that when I run into a difficulty I can look at it and say 'I wonder what J. P. would do.' "

Mrs. Pratt concedes candidly, "I have no modesty whatever where my husband is concerned. First of all, he is a good doctor, but there is more than skill that goes into being a good doctor. He has warmth, kindliness, sympathy, and a wonderful understanding of women. He likes women! He is always on their side. No matter what they have done, he believes that they would do no wrong unless they were provoked into it. He plays the role of big brother, father, counselor, husband, and father confessor to all his patients. When a patient has a problem, he will sit very still for a long time while he projects himself into her mind trying to understand her emotions and her reactions and then find a solution for her. Ninety-nine times out of a hundred he is right. Once our daughter asked her dad's advice about a problem, and she said, 'Mother, Dad's solution does not seen right now, but I am afraid to go against his advice because I know that he will be right in the end.' He gives long and considered thought to every problem that presents itself. He never makes snap judgments. He has the wonderful faculty of putting himself in the other person's place."

She adds: "He never tries to change anyone. He will advise them but never tell them what they 'ought' to do. He enjoys people for the individuals they are and not for what they might be. My husband has never criticized me. I know that sounds ridiculous and impossible but it is true. Not that I don't deserve it. He has never said to me, 'Why did you do that?' He recognizes me as an adult, with all the human frailties of a woman, and he likes me not because of them but in spite of them. I admire my husband tremendously as a man, a doctor, a father, and a husband. Knowing him as a fine man, possessed of unquenchable zest and zeal, I know that he will go on practicing medicine as long as he lives and I pray that I will have my husband as long as I live."

HONORS

It has been mentioned that Dr. Pratt was president of the Association for the Study of the Internal Secretions. He has also been president of the Michigan Obstetric and Gynecologic Society (1932), and of the Central Association of Obstetricians, Gynecologists and Abdominal Surgeons (1936); vice president of the American Gynecologic Society (1947), and a member of the Association of Anatomists, and a member of the House of Delegates of the American Medical Association (1941-1948); and for the past 10 years he has been president of the Foundation of the American Association of Obstetricians and Gynecologists.

* * * * *

While waiting for the bus to take me to the air station, I spent a pleasant hour in a downtown club. Behind the bar was the best informed and most pessimistic of the *cognoscenti* previously mentioned. Detroit is in trouble, he said; and since we were alone and he was in a conversational mood, he proceeded to prove his point with unemployment figures and statistics of the removal of automobile plants to Flint and elsewhere. The Tigers are in trouble, he said, and elaborated his dire prediction with a wealth of baseball details. Agreeable to his mood, I mentioned the empty boarded-up stores I had seen near Henry Ford Hospital.

"Wayne University has bought up all that part of the city to make a big campus," the man said, and added unexpectedly: "Liberal education is in trouble."

"How does that figure?" I asked.

"You know what all this expansion is for?

To mass produce scientists. Assembly-line robots."

I considered this for a moment. There came to mind Dr. Finney, who practiced equally the art and the science of surgery; Oliver Wendell Holmes, presiding at a feast of science and letters; Sir William Osler, wise in medicine and the humanities. I might have thought of many others, from Hippocrates to Harvey Cushing, but I did not. I thought of Jean Paul Pratt, the Henry Ford Hospital gynecologist who sees medical problems broadly and his patients not merely as mechanisms, but as human beings. How greatly he must have influenced his colleagues and, more particularly, the numerous residents now spread out across the country.

"Don't be sure," I replied. "People may surprise you."

My cynical acquaintance raised his eyebrows, and I raised my glass: to a doctor who is friend and advisor to his patients.

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PRESENT STATUS OF OPTICAL CORNEAL GRAFTS

JOHN V. BALIAN, M.D.*

The prime consideration of optical keratoplasty is maintenance of corneal transparency. All too frequently, corneal transplants become clouded even when the surgical technique has seemed to leave nothing to be desired. Some of the donor and host factors influencing final graft clarity are yet to be fully understood, but certain principles have become apparent. It is the primary purpose of this paper to review what is "known" along this line, together with some of the less well established or frankly speculative aspects.

Reports on results with optical keratoplasty are numerous, and rather variable, there being general lack of uniformity of material, criteria of success, and standards of procedure. A reasonably typical report in 1950 stated that of 241 keratoplasties 16.4% resulted in worse vision, 30.3% remained unchanged, and 53% resulted in improved vision.[1,2]

Gross comparison of various selected series suggests the following corneal conditions to be favorable for keratoplasty (in order): 1) Non-edematous "degenerations"; 2) residue of chronic infections or non-specific inflammations; 3) traumatic lesions. Edematous degenerations appear strongly to have the least favorable prognosis, while grafts for keratoconus, a "dry" avascular "degeneration" usually confined to the central portion of the cornea, yield the most satisfactory visual results.

For best results, both the donor cornea and the recipient bed need be transparent. The importance of corneal transparency lies in the biophysical implications of the state: Viability, critical hydration, normal intraocular pressure, intact endothelium, and precise structural arrangement of stromal fibers and cementing substances. The significance of the factors mentioned which determine corneal transparency lies in the role they play upon the ultimate fate of the graft.

The weight of evidence supports the view that the cells of the graft are replaced by the host (epithelial cells almost immediately, stromal cells and endothelial cells very gradually) but that Bowman's membrane, collagen framework of the stroma, and Descemet's membrane persist morphologically. Cell death occurs at a considerably increased rate after keratoplasty, but even so, goodly proportions of the donor cells remain viable usually for months, possibly for years. Simultaneous death of all stromal cells in the graft does not occur.[3] It is felt that the *speed* of replacement of donor stromal cells by host cells is inversely correlated with the "success" of the graft.[4]

The orderly regeneration of normal transparent cornea can be impeded or prevented by structural and metabolic disturbances of both the recipient bed and donor cornea. This may occur in at least three ways:

I. Immunological response of host to donor tissue

The necessity of utilizing homografts carries with it the possibility of an undesirable immunobiological response of the host to the donor cornea. Fortunately, there is low antigenicity of corneal tissue, attributable to its avascularity and cellular paucity. However, hypersensitivity reactions do occur and may lead to vascularization,

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infiltration and permanent clouding of the graft. Vascularization of the graft must take place before such a reaction exhibits the leukocytic, lymphocytic and fibroblastic infiltration which is found in other unacceptable homograft tissue.

It has been demonstrated in rabbits that sensitization can result in corneal clouding up to a period of eight weeks after keratoplasty.[5] Experiments have shown that graft clouding is almost inevitable if a piece of skin from a donor rabbit is implanted under the abdomen of the recipient animal two weeks prior, concomitant with or even shortly following the actual keratoplasty.

Corneal vascularization seems (usually) necessary for opacification of a human homograft on the basis of a hypersensitivity reaction. The presence of adventitious corneal vessels certainly appears to increase the likelihood of such reaction. Corneal stromal cells will not die following intracorneal injection of an antigen (e.g., horse serum) to which the animal (e.g., rabbit) has been highly sensitized until blood vessels grow into immediate proximity to the particular corneal stromal cells under consideration. This may well be due to the low antibody titre of non-vascularized cornea.[6] Preoperative treatment of vascularization by surgical means has its place, although revascularization occurs only too often. Irradiation methods, once widely used, now appear on the whole to have been worse than useless.

The role of the donor cells in eliciting the hypersensitivity reaction seems dependent upon their number and their survival. The corneal epithelium which consists of five or six layers of cells, added to the stromal tissue, does appear to increase the tissue reaction to the graft in laboratory animals.[7] A potential immunological hazard is evident when the corneal tissue of the very young is utilized, since keratocytes are more numerous in the young cornea. In addition, the direct relationship of graft size to the number of cells must be remembered in light of this problem.

While considerable experimental evidence supports the view that a hypersensitivity reaction can underly delayed clouding of corneal grafts, the exact nature and cause(s) of the reaction in human corneal homografts remain to be elucidated. Race and sex are considered insignificant in the selection of donor material, while blood type incompatibility (ABO, Rh) does not alter the incidence of success.[8]

II. Physical chemical aspects of donor and host cornea

Consideration of the donor cornea as a precise architectural framework upon which the regenerating host tissue is dependent would suggest that any divergence from structural normality by the donor cornea would unfavorably influence the final clarity of the graft. The orderly and gradual replacement of donor elements can be prevented by dissimilarity in the thickness of donor and recipient corneas. Further, the precise apposition of the host and donor corneas is important in keeping the graft-host interval relatively impervious to water and vascular ingrowth, while the integrity of the endothelial surface plays an important role in the critical hydration of the graft. Cogan[9] attributes vascularization of the cornea to a reduction in the compactness of the tissue in the vicinity of pre-existing vessels. The presence of even one large vascular trunk in the cornea is considered a hazard to optical keratoplasty and emphasizes the need for a normal corneal bed.

In summary, presence of scar tissue can impede the regenerative process by constituting a "stumbling block" to the migrating host cells, while the presence of adventitious blood vessels in the normally avascular cornea signifies a derangement of physical chemical factors underlying corneal transparency.

III. Metabolic deficiencies of host cornea

In the broadest sense, at least two factors would appear to be involved in the resumption of normal metabolic activity following keratoplasty: 1) Supply of metabolites via limbal blood vessels, 2) normal host cells. Tracer studies reveal that there is a negative balance of sulfur-containing amino acids in the donor cornea following transplantation. An intact vascular plexus of the limbus is necessary if amino acids and others metabolites are to reach the regenerating cornea. In addition, intracellular enzymes, on which the synthesis of protein and ground substance depends, are deficient if the corneal cells of the host are quantitatively or qualitatively abnormal.[10]

The importance of structural integrity and normal viability is appreciated and has resulted in much experimental effort toward the long-term storage of corneal graft tissue. Factors which influence the viability of stored cornea are temperature, duration of storage, pH of the storage solution, nature of storage medium and the state of the cornea upon enucleation. At present, refrigeration at 4°C in a moist chamber yields fairly clear corneal material if used within about 48 hours. A more important factor is how soon corneal material is refrigerated after the death of the donor. Newer methods of preservation include pretreatment in varying concentrations of glycerine and saline and deepfreezing at -79°C.[11] In the end, the most important criterion of suitability of donor material is felt to be its transparency at the time of keratoplasty.[12]

SUMMARY

The many problems involved in successful optical keratoplasty are being more thoroughly appreciated and, especially from the technical standpoint, are being resolved. Further elucidation of the various biologic and physicochemical factors, relative to the graft and the recipient bed, which cause opacification in corneal grafts can be expected to increase the applicability of the procedure. Careful case selection at the present time, as evidenced by the success in keratoconus, permits reasonably good prognostication.

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THE STAPHYLOCOCCI

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Staphylococcal infections have been the topic of considerable discussion during the last decade. This problem has assumed great prominence chiefly because infections due to these organisms have remained a serious therapeutic problem in spite of the large number of antimicrobial agents presently available. The adaptability of the staphylococci to various antibiotics is relatively unique among the organisms which commonly produce disease in man. Consequently there is an ever increasing number of organisms which are resistant to many antibiotics, especially within the hospital community.

The ubiquitous nature of various strains of staphylococci has created a tremendous problem for all concerned. Thus, it should be pointed out that there are a multiplicity of channels by which the offending organism can be spread within the hospital. Therefore, in order to control this problem it is absolutely essential that the routes of transmission be recognized and that antibiotics and immunization procedure be a second line of defense.

During the last two years we have made several bacteriologic surveys of staphylococcal infections in the following hospital areas:

1. Pediatric service including the nursery.
2. Orthopedic service.
3. General surgery.
4. Neurosurgery.

The bacteriologic studies included the isolation and identification of staphylococci, antibiograms and bacteriophage typing.

MATERIALS AND METHODS

The bacteriologic specimens were routinely inoculated onto the surface of sheep blood agar plates which were incubated aerobically at 37°C. The staphylococci were isolated and characterized on the basis of colony morphology, hemolysis, pigmentation, mannitol fermentation, lipase activity, coagulase testing, antibiograms, and phage typing whenever it was deemed necessary.

Since there is a high correlation between coagulase production and human virulence, the coagulase test was performed on all staphylococci regardless of pigment and hemolysin production. However, it should be emphasized that coagulase is merely another index of the broad array of biologic properties which characterize strains of pathogenic staphylococci. The actual factors responsible for virulence are merely associated with coagulase production.

Antobiograms were obtained by the disk procedure and in many instances the tube dilution technique was also used. The antibiotic susceptibility patterns have

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been performed with the following antibiotics penicillin, streptomycin, chloramphenicol, tetracycline, erythromycin, oleandomycin, novobiocin, ristocetin, vancomycin, and bacitracin.

Bacteriophage typing was performed on isolates obtained from patients and hospital personnel selected for epidemiological evaluation. The phage typing has been performed by Dr. William Ferguson's group at the Department of Health Laboratories, Lansing. The bacteriophage procedure was based on the following classification:

Group I	29, 52, 52A, 79, 80, (81)
Group II	3A, 3B, 3C, 55, 71
Group III	6, 7, VA4 (83), *42B*, 42E, 47, 53, 54, 70, 73, 75, 77, (81)
Group IV	42D
Miscellaneous	31, 42C, 44, 44A, 29, 39, 47C, 523, 187, (81)

The phage typing of staphylococci is limited by the following factors:

1. It is not possible to type all the strains of *S. aureus* with the phages now available.

2. The consideration that certain phages (ie. 42B) have a broad lytic pattern and will probably be eliminated in phage testing.

3. Certain strains of staphylococci may be considered variants if their phage pattern is slightly different.

RESULTS

Pediatric service including the nursery

The isolation and identification of organisms from infants with pyoderma has been conducted on several occasions. Our data shows that the most common strain of *staphylococcus* was the 42B/47C/52/80/81 type which is one of the "epidemic strains". In our experience the occurrence of pyoderma in the newborn has been associated with maternal postpartum breast abscesses as well as subsequent suppurative disease in other family members. The records again show the prevalence of this same strain in the majority of the cultures obtained from their lesions and nasopharynx. Thus the oragnism appears to be transmitted freely within the family group.

In nearly every nursery survey, where doctors, nurses and personnel have been investigated, the "epidemic strain" has been isolated from the nasopharynx and skin of varying percentages of the nursery staff. The significance of these findings have been interpreted differently by various authors.[1] It is extremely likely that there are multiple routes of transmission and chief among these considerations based on our studies is probably the personnel — to infant to personnel route. As the epidemic procedes, a mixture of several modes of transmission (ie. infant to environment to infant) assist in the dissemination of the infection in a cyclic manner.

We have gained some knowledge by phage typing strains isolated from other pediatric areas. However, the majority of these isolates were *not* of the epidemic variety. The following is a list of the phage types which have been isolated from pediatric patients:

1. 6/47/53/77/VA4
2. Untypable
3. 80/81
4. 7/47

More than 50% of the strains in one particular study were not typable by the phage procedure. The majority of the remainder were of the Group III variety.

General surgery — Neuro surgery — Orthopedic surgery

During the past two years we have had the occasion to study the phage types of *staphylococcus aureus* isolated from surgical patients in units throughout the hospital. In some units the infection rate with this organism was considered to be higher than usual. Naso-pharyngeal swabs of the surgical teams were obtained in an attempt to evaluate the carrier state. Furthermore, surgical instruments, gloves and other articles in the operating areas were cultured. Phage typing of coagulase positive *staphylococcus aureus* was performed.

The data shows that 40% of the strains belonged to phage Group III; 15% consisted of two types of epidemic strains: 42B/47C/52/80/81 (Group I) and 7/77 (Group III). The latter has been isolated more frequently from wound infections by various groups in this state. As many as 45% of the strains in some series were untypable. A detailed analysis of the results within each surgical unit showed very little correlation between phage types of nasal carriers and the isolates from wound infections. Bacteriologic surveys of skin, clothing and various articles failed to positively identify the route of transmission for surgical infections.

Antibiograms and Phage Patterns

The staphylococci are often resistant to many antibiotics. Approximately 80% of all clinical isolates in this hospital are resistant to penicillin and 40% are resistant to tetracycline.[4] The results in Table I shows the antibiotic sensitivity and phage patterns of the staphylococcal strains which were phage typed. This data shows that a large percentage of strains were resistant to penicillin and tetracycline. These

Table I

Bacteriophage and Antibiotic Patterns of Staphylococci

Phage pattern	Per cent sensitive to		Resistant to Penicillin Tetracycline
	Penicillin	Tetracycline	
Group I	17	24	59
Group II	60	0	40
Group III	18	18	64
Group IV	—	—	—
Miscellaneous	50	50	50

results re-emphasize the absolute necessity for requesting sensitivity tests on all staphylococci obtained from patients with clinical manifestations of infection.

DISCUSSION

Although the completeness of our observations is less than optimal, there is no doubt in our mind that the so-called epidemic strain (42B/47C/52/80/81) is invariably associated with pyoderma among newborn infants during their hospital stay, and that this strain is subsequently responsible for breast abscesses among nursing mothers as well as a variety of subcutaneous abscesses etc. in the family group. Thus, it is extremely important to apply methods of prevention and control in accordance with many published reports,[2,3] especially since infants in nurseries represent a population which is highly susceptible to epidemics of staphylococcal infections.

Perhaps the greatest single factor in controlling infections conveyed by various methods is that of educating the staff to seriously consider all the precautions which may avoid staphylococcal infections.

Phage typing of *staphylococcus aureus* was developed by Fisk[5] as well as Wilson and Atkinson.[6] The procedure has been employed extensively during the last few years in epidemiological studies. Although difficulties in interpretation do occur, especially with strains that are susceptible only to low dilution of phage, the method has proved to be very helpful to the epidemiologist.

A comparison has been made between bacteriophage and serological typing procedures by Oeding and Williams[7] for identifying various types of coagulase-positive staphylococci. They state that "the principal advantages of phage-typing are the facts that it is able to recognize more types than the serological method, and that the distinctions between the types are based on a greater number of different reactions. The advantages of the serological method are the smaller number of untypable strains and its greater technical simplicity". These procedures together with the fluorescent antibody technique are being evaluated experimentally in our laboratory at this time.

SUMMARY

An analysis of the phage patterns of the coagulase positive staphylococci isolated at Henry Ford Hospital shows that a large percentage of the typable strains are members of phage Group I or III. The majority of isolates obtained from infants, mothers and the family group are members of Group I whereas only 15% of the isolates from the surgical wound infections belonged to this group.

The sensitivity patterns of the isolates is analyzed. Fifty per cent of the strains are resistant to both penicillin and tetracycline.

The nasal carrier rate of doctors, nurses, etc. shows a tremendous variation (14 — 50%) among various groups studied.

The principal advantage of phage-typing is that the distinction between types can be of some epidemiological value.

Most of the staphylococcal infections which appeared during hospitalization or shortly after discharge were presumably the result of cross-infection. The majority of these infections are theoretically preventable and therefore the institution of a program for the prevention of cross-contamination (aseptic technique) is extremely necessary.

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INTERRELATIONSHIP BETWEEN BRAIN DAMAGING PROCESSES AND PEPTIC ULCERATION, PERFORATION AND HEMORRHAGE

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The existence of a relationship between brain damaging processes and peptic ulceration with or without perforation and hemorrhage was first documented by Cushing in this country in 1932.[1] Cushing had the possibility of this interrelationship rather dramatically called to his attention when three of his patients upon whom he had operated for cerebellar tumors subsequently developed peptic ulcers with perforation or hemorrhage and died from these events. Because these case reports are so interesting and do emphasize what we are discussing, I will describe two of them very briefly.

The first case was that of a 34 year old bank clerk who was investigated because of a choked disc and other evidences of brain tumor. These symptoms were cerebellar and there was a subsequent suboccipital exploration under ether anesthesia. A subcortical angioblastoma was found in the right cerebellar hemisphere. Evidently, there had been no preoperative symptoms relative to the stomach except those thought to be created by the cerebellar tumor, namely, some nausea and vomiting, associated with dizziness. However, immediately after the operation, when the patient first awakened, he complained of abdominal discomfort. The abdomen appeared somewhat stiff and tender but no special significance was attached to this. The patient was sedated with morphine but he grew increasingly worse, became cyanotic and expired 24 hours after the operation. At postmortem examination, it was found that the peritoneal cavity was full of a large amount of turbid fluid and the stomach showed three circular perforations halfway between the cardia and the pylorus on the lesser curvature. These ulcers showed no previous indications of inflammatory reaction but the mucosa of the entire stomach appeared as if the patient had consumed a corrosive poison.

The second case was that of a 34 year old engineer who was operated on because of a full-blown picture of cerebellar tumor — this had existed for five years. There had been occasional attacks of vomiting. In this case, the patient was operated on and a median tumor was disclosed which was an astrocytoma with a long tongue projecting from the posterior fossa far into the spinal canal. A laminectomy of the axis and atlas was necessary to expose the lower pole of the tumor. Postoperatively, the patient appeared to do very well. Two days after the operation, a sudden, violent epigastric pain spread over the abdomen and into the shoulders. There had been no previous evidence of any abdominal complication and this episode was considered pleuritic in nature. The patient was sedated with morphine. However, the patient developed hyperthermia of 106.2° and expired on the fourth postoperative day. In this case, the postmortem examination showed the peritoneal cavity to be filled with 110 cc of reddish brown fluid and there was evidence of a generalized, diffuse fibrinoplastic peritonitis. Two perforations of irregular shape were found in the wall of the duodenum about three centimeters distal to the pylorus. Further examination disclosed no evidence to suggest these ulcerations had been previously present.

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Cushing mentions that the circumstances wihch permit one to demonstrate mucosal lesions after an intracranial operation are not often combined and hence may account for scarcity of such reports in the past. These same factors would be involved today and thus will be mentioned:

1. An opertaion of the sort necessary to produce lesions, such as an intracranial operation.
2. A postoperative fatality at the proper time to find a lesion because it is well known that if even a short period of time passes, the lesions may heal over.
3. Permission after a fatality for an unrestricted autopsy, and —
4. A more careful scrutiny of the gastroduodenal mucosa than is customary, particularly when the obvious cause of death lies elsewhere.

Cushing also calls attention to several other cases involving intracranial conditions other than actual tumors or operations. One such case was that of a 32 year old woman with malignant hypertension who pursued a course of progressive cardiac failure and died. Just prior to death, there was hyperthermia of 104°. At autopsy, the gastric mucosa was found to be intensely injected and to contain numerous small star-shaped recent ulcerations, more marked on the lesser curvature, to many of which fairly recent blood clots were adherent. Apparently the patient had not been in uremia.

A second case of this type was that of a 44 year old man admitted to the hospital as a brain tumor suspect but who was found to have malignant hypertension with choked discs, arteriosclerosis and cardiac hypertrophy. In the study, the patient did have ventriculograms, which were normal. Five days following this, there was sudden hematemesis with vomiting of 500 cc of blood and a repeated hematemesis the next day with a loss of another 800 cc of blood. Several days after this, the patient had sudden, severe epigastric pain and was explored, whereupon a perforation of the posterior wall of the stomach one centimeter in diameter and 8 centimeters proximal to the pylorus was found. This was surgically closed but the patient died several days later with a temperature of 104°. Autopsy revealed that the sutures closing the perforation had been dissolved and the stomach was in shreds from autodigestion. The pancreas had become involved and there was extensive fat necrosis as well.

Cushing did speculate on the occurrence of chronic ulceration with intercerebral lesions and presented cases in support of this thought. One case was that of a 9 year old child who was operated upon for removal of a median cerebellar medulloblastoma with a wide opening made in the fourth ventricle. The patient subsequently had repeated courses of radiation therapy. However, the patient finally succumbed two years later. At autopsy, in addition to the intraventricular involment by the tumor, there was noted a small duodenal ulcer crater 3 centimeters below the pylorus. Microscopic examination of the ulcer showed that it was characterized by a crater extending down to the muscularis with margins deep and slightly undermined. On its floor, there was a narrow zone of dense hyalinized connective tissue and in one region some fibrin and blood cells. Scar tissue at the rim of the ulcer showed chronic inflammatory cell infiltration.

An additional case in this regard was that of a 25 year old man who had a tumor of the third ventricle, demonstrated by ventirculography, causing pressure symptoms associated with gastrointestinal disturbance. He had several episodes of radiation to the lesion, each with marked improvement. However, within three days of the most recent treatment, which was some years after the tumor was first found, he developed ulcer symptoms at which time a barium study showed evidence of the ulcer.

In an attempt to find a reasonable explanation for these acute and probably chronic ulcerations involving the esophagus, stomach and duodenum, particularly those mentioned in the first three cases, Cushing conducted an extensive review of the literature on the neurogenic aspects of ulcer pathogenesis. This review led him to believe that there was a parasympathetic center in the diencephalon. From this center fiber tracts passed backward to relay with the cranial anatomic stations of the mid-brain and medulla of which the vagus nucleus is by far the most important. Experimental lesions anywhere in the intracranial course of these fiber tracts, from the anterior hypothalamus to the vagal center, presumably from parasympathetic stimulation, are prone to cause gastric erosions, perforations and hemorrhage. Intracranial injuries and diseases affecting these same basilar regions of the brain are known to be accompanied by ulcerative lesions of the upper alimentary canal. Cushing believed, therefore, that perforations following cerebellar operations were produced in like fashion by an irritative disturbance of tracts or vagal centers in the brain stem. Further, Cushing felt that highly strung persons who incline to the form of nervous instability classified as parasympathetic (vagotonic) through emotion or depressed emotion incidental to continued worry, anxiety and heavy responsibility allied with other factors, such as irregular meals and excessive use of alcohol, are particularly prone to have chronic digestive disturbances with hyperacidity, often leading to ulcer. This, of course, is the reasoning behind vagotomy done with subtotal gastric resection for treatment of peptic ulcerations.

Davis, Wetzel and Davis[2] from Northwestern University, in 1955, aware of the previous report by Cushing and knowing of the apparent increase in frequency and gravity of acute alimentary tract ulceration and hemorrhage in the neurosurgical period, determined to study a large series of neurosurgical patients to evaluate the incidence, natural history and possible mechanisms involved in these complications. An analysis of 7,000 operative and clinical records distributed over 30 years revealed 48 examples of acute upper gastrointestinal ulceration or hemorrhage during the post-neurosurgical period, an incidence of 0.7%. In a series of 943 craniotomies, there were 24 instances in which this complication occurred; in 350 suboccipital craniectomies, it was found in the postoperative course of 7 patients. A careful inventory of gastrointestinal tract symptoms was made in all patients prior to surgery and in 8 cases there were pre-existing complaints of varying severity. These same 8 patients had acute fatal or nearly fatal episodes of hematemesis following the neurosurgical operations. There were 12 patients who, initially, had a smooth post-operative course and who would have recovered well from the effects of the neurosurgical procedure had it not been for unexpected, sudden and massive gastrointestinal tract hemorrhage, which was considered to have led directly to their death. In a

total of 30 deaths from various causes in this series, 24 autopsies were performed and in 15 instances an ulceration was present or the cause of the gastrointestinal hemorrhage was determined. The ulcerations which were seen extended through the muscularis mucosae of the involved structure and were grossly and microscopically characterized by lack of fibrosis and induration.

A correlation of the anatomic position of the lesion in the nervous system with the upper alimentary tract hemorrhage or ulceration in 12 patients in whom death was directly attributed to these complications revealed: 3 patients with frontal lobe glioblastoma, acoustic neurinoma in 2 cases, pituitary adenoma in 2 cases, frontal lobe metastatic carcinoma of the lung, posterior fossa metastatic renal carcinoma, cervical spinal cord arachnoiditis, and a diagnosis of no cerebellar pathology, each in one patient.

On the basis of this data, the authors concluded that upper gastrointestinal tract hemorrhage and ulceration following neurosurgical procedures are frequently highly fatal surgical complications. There would appear to be no correlation between the histologic character of the pathology of the nervous system and the occurrence of the lesions in the gastrointestinal tract. Central nervous system pathology was not a prerequisite for these gastrointestinal complications since they were encountered following such procedures as laminectomy, hemilaminectomy and trigeminal neurectomy. The authors were impressed that in this series of 48 patients disease of the cerebral hemispheres, and in particular the frontal lobe, was of more frequent occurrence than involvement of the diencephalon or the posterior fossa. They felt that it was not probable that any extensive lesion would impinge on the hypothalamic frontal pathways without also destroying other fiber tracts, so that they felt it would be doubtful that diencephalic lesions could be solely responsible for producing an autonomic imbalance leading to the gastric ulceration, perforation or hemorrhage.

Davis, et al,[2] make note of a recent publication by French[3] and his associates in which they observed a group of patients with similar severe postneurosurgical hematemesis and gastrointestinal tract ulceration. In addition, they presented experimental data in which carefully oriented stereotactically placed hypothalamic lesions were created with the Clarek apparatus. A group of 13 cats were used and ulceration and/or hemorrhage occurred in all but one animal. Hence, they concluded that lesions which involve the hypothalamus or its afferent or efferent pathways predisposed the patient to gastrointestinal disease, which in turn was precipitated by the stress of the illness and/or the trauma of surgery. This was not in agreement, however, with the previous work of Martin and Schnedorf[4], who observed that localized lesions made by the Horsley-Clarke apparatus in the hypothalamic area of 7 monkeys and 40 cats failed to reveal any mucosal changes in the gastrointestinal tracts which could be ascribed to the lesion. Further, this was not in agreement with the recent findings of Davis et al[2] in which small, destructive hypothalamic lesions were made in a group of 15 cats using the Clarke Stereotactic apparatus. In this group of 15 cats there was no gastrointestinal tract pathology following discrete anterior and posterior hypothalamic destructive lesions. This data, plus the fact that gastrointestinal lesions occurred in 7 patients in their series in which the surgical procedure was neither intracranial in location nor was the central nervous system exposed at any

time, led Davis et al[2] to believe that interruption of a disease process of the frontal lobe connection of the hypothalamus itself or projections from this structure in the posterior fossa were not essential for production of gastrointestinal complications. They rather suggested that the gastrointestinal tract ulceration and hemorrhage represent an extreme pathophysiologic response to the physical stress at surgery, wherever its location.

It is difficult to reconcile the divergent results of these studies with the Clarke apparatus.

Watson and Netsky[5] from the Montefiore Hospital in New York observed as others had that there had been considerable interest in the concept of neurosurgical postoperative ulcerations of the gastrointestinal tract. They felt that too little attention had been given to the occurrence of upper alimentary tract disorders in chronic neurologic diseases not created by intracranial surgery. They presented 6 cases to bring out their point.

The first case was that of a 36 year old woman who was found to have multiple sclerosis. Five months after the diagnosis was made, the woman had a sudden, unheralded, acute abdominal episode suggesting ruptured viscus. It was shown by laparotomy that there was a perforation high on the posterior wall of the stomach. This perforation was surgically closed but the patient died in hyperthermia and shock 24 hours later. Necropsy revealed a recurrence of an ulcer and microscopic examination of the nervous tissue showed lesions of different size and age thought to be typical of multiple sclerosis.

The second case was that of a 33 year old woman who was to have a right lower lobectomy for pulmonary tuberculosis, but during the induction phase of the anesthesia, the patient was apneic for four minutes. Afterward the patient remained in deep coma with occasional convulsive movements and died 15 days later in a hyperthermic state. At autopsy there was found to be widespread loss in neurons and there were infarctions involving the cortex anterior to the thalamic nuclei, the posterior portion of the hypothalamus, an area inferior to the geniculate bodies and areas involving the spinal cord and cerebellum. These changes were thought to be secondary to anoxia. Also, it was found that there were two ulcers in the duodenum, one centimeter and two centimeters, respectively, in circumference. One of these had perforated.

The third case was that of a 73 year old man who had a slowly occluding right middle cerebral artery. Arteriography showed no filling in the cervical portion of the right internal carotid artery. The patient died subsequently with a terminal temperature of 103°. At necropsy, the cardia and proximal portion of the stomach were malacic and a gaping, 3 centimeter perforated ulcer was found in the stomach. Also examination of the brain revealed massive infarction of the right cerebral hemisphere accompanying thrombosis of the internal carotid artery.

A fourth case was that of a 36 year old man who was shown by craniotomy to have a metastatic melanoma. He had previously had a pigmented lesion removed from his back some 8 years earlier. The patient had radiotherapy and some attempt at decompression of intracranial pressure by ventriculostomy with polyethylene tubing

and repeated lumbar punctures, but he died in a hyperthermic state about a month later. At the time of autopsy, he was noted to have dark fluid in both pleural spaces with necrosis and digestion of the lower portion of the esophagus with associated nearby ulcerations seen. It was thought that there was neoplastic involvement of the hypothalamus and related structures.

The fifth case was that of a 47 year old man with multiple sclerosis who, over a period of five years, gradually developed spastic quadriparesis and severe ataxia. He had for several years had postprandial epigastric distress and tenderness, relieved by vomiting, but repeated x-ray studies showed only delayed gastric emptying. A strict Sippy diet did help the problem. However, at age 61, 14 years after his first diagnosis of having multiple sclerosis was made, he died suddenly following an onset of collapse. Autopsy showed that there had been a hemorrhage from an ulcer in the duodenum just beyond the pylorus. In the brain, internal hydrocephalus, without obstruction, was present and microscopic examination showed demyelinated zones in various areas compatible with the diagnosis of multiple sclerosis. The lesions were noted to include the hypothalamus.

The last case is that of a 68 year old man who developed a left hemiplegia. There were several procedures done, including ventriculography, lumbar puncture and burr holes for a possible subdural hematoma. The patient subsequently became hyperthermic and died 8 days later. At autopsy, it was found that the right cerebral hemisphere was swollen and there was an ischemic infarction of the basal surfaces of the right frontal and occipital lobes with a fresh thrombus seen in the cavernous sinus portion of the right internal carotid. In the duodenum there were three bloody superficial ulcerations and fresh blood in the small and large intestines. Thus, this patient had had a thrombosis of the right internal carotid artery associated with ulceration and hemorrhage of the stomach.

In addition to these six cases presented, the authors summarized the literature and found 38 cases in which there had been combined neurologic and gastrointestinal disorders and which were accompanied by complete necropsy examination. The intracranial diseases which led to the gastrointestinal changes are listed as follows:

Table I

Intracranial Diseases Associated With Gastrointestinal Changes

Suppurative Meningitis	9
Vascular Accidents	8
Primary or Metastatic tumors	7
Head injury or birth trauma	6
Viral Encephalitis or Poliomyelitis	4
Asphyxia	2
Neonatal Convulsions	1
Gun-shot wound involving the head	1

To the above table, one may add the six cases just described; namely, that of two cases of multiple sclerosis, two cerebral vascular thromboses and one case each of metastatic melanoma and asphyxia.

It was felt that these cases were of interest because of the ante mortem symptoms of alimentary tract disorder. In seven of the cases, there was terminal hematemesis and in three cases there were sufficient abdominal symptoms to cause clinical concern.

In one case there was a laparotomy because of acute abdominal distress arising from perforation of the stomach.

In the cases surveyed, there was no case with restriction of the neurologic disease to the hypothalamus alone; in all, there was associated pathlogic change in adjacent or distant regions of the brain. Similar observations were made upon postoperative brain tumor cases. Multiple metastases, widespread changes associated with increased intracranial pressure, bilateral lesions secondary to cerebral arteriosclerosis, etc. were found in all cases, in addition to the primary lesion. The sites of major disease processes are shown in the following table:

Table II

Intracranial Diseases Associated With Gastrointestinal Changes

Location of Intracranial Disease	
Meninges	25
Cortex	37
Sub-cortex	28
Hypothalamus	30
Pons	16
Medulla	9

From this data, since no case lesion could be confined soley to the diencephalon, it was suggested that a question might be raised whether or not a higher center may be involved in the neurologic axis leading to gastrointestinal disorders. It was suggested that it might be possible to by-pass the hypothalamus entirely upon occasion. Thus, the authors modified the concept of lesions involving the hypothalamus and tracts leading to the vagal nuclei, as expressed by Cushing, to include the concept of a higher center, that is, a cortical or sub-cortical involvement leading to the hypothalamus and thus to the vagal nuclei. In this modified concept, the idea is that the cortex moderates or damps the lower centers so that with the later allowed unbridled activity because of cortical centers or pathways not properly functioning, excessive parasympathetic effect could thereby be wrecked upon the viscera. This excess becomes the modus operandi of ulceration and malacia of the gastrointestinal tract.

To this point, we have been concerned with reviewing data demonstrating the relationship between intracranial disease and/or neurosurgical procedures and acute ulceration, perforation, and hemorrhage of the gastrointestinal tract. It would appear interesting to present some data further complicating the picture of neurogenic induction of gastrointestinal disease. Gray[4] and associates from the Harvard Medical School in 1953 demonstrated that the administration of adrenocorticotropic hormone and cortisone, after a period of days or weeks induced an increase in the basal and nocturnal gastric secretion of hydrochloric acid and pepsin approximating 200% with a similar concomitant increase in uropepsin excretion. Such patients experienced epigastric distress during hormone therapy or developed peptic ulcers, reactivation of previous ulcers, hemorrhage or perforations, and demonstrated, coincidentally, peak uropepsin excretion and increased gastric acid and pepsin secretion in the ulcer range. Vagotomy did not alter the response to adrenocortical or cortisone administration. They further noted that stimulation of the hypothalamus in dogs produced significant increases in uropepsin excretion and that patients with hypopituitarism and hypoadrenal function (Addison's disease) demonstrated low uropepsin excretion. Further, patients with adrenal and pituitary hyperactivity excreted increased amounts

of uropepsin. These data suggest that chronic emotional and physical stress stimulate the stomach to secrete increased acid and pepsin by way of a humeral mechanism involving the hypothalamic-pituitary-adrenal-gastric axis independent of the vagus nerve or the gastric antrum.

In regard to the idea of stress as the cause of gastrointestinal ulceration, it is interesting to mention the work of MacDonnell and McCloskey[7] of Philadelphia in 1953. They point out that while the association of acute ulcerations of the peptic type were observed by Cushing in 1932 in association with intracranial problems, and by Curling[8] in 1842 in association with burns, no one has paid much attention to the relationship of acute peptic ulcers to other pathologic changes in the body. These authors made a study of 1781 consecutive autopsies performed and found acute peptic ulcers in eight of 243 patients who died following operations performed elsewhere than on the central nervous system, an incidence of 3.24%. Similar ulcerations were found in five of 109 patients in whom central nervous system lesions were found at autopsies, an incidence of 2.78%.

Their conclusion is that since these two percentages are so similar acute peptic ulcers which occur in association with surgical procedures, burns, intracranial lesions, etc., are simply one result of the body's exposure to stress.

Further in regard to stress, it is interesting to review some recent data concerning Curling ulcers. This is reported by Hummel et al[9] of the Medical Corps of the United States Army in 1957, in which they studied 1,000 burned patients admitted to the Brook Army Hospital over a period of 6-½ years. Of these, 20 developed Curling ulcer, 17 of these were among 80 burned patients who died. Of the 20 patients who were burned and who developed gastrointestinal ulcerations, 7 were asymptomatic, hemorrhage occurred in 10 and 3 had abdominal pain. The majority of the ulcers were in the duodenum and in only 7 cases were the ulcerations multiple. The burned patients were studied for uropepsin and gastric acidity. Gastric acidity was quite variable but tended to be higher in the more severely burned patients. Elevated uropepsin levels and gastric acidity, however, were of no diagnostic value in predicting which patients who were burned would develop the ulcerations.

Because it concerns stress and shock, as well as the gastrointestinal implications of bulbar lesions, it is of interest to bring out the data presented by Schaberg, Hildes and Alcock[10] in 1954, in which they made the observation that of 480 cases with clinical involvement by poliomyelitis of the bulbar nuclei, upper gastrointestinal tract bleeding was observed in 34 cases; of these 11 survived and 6 died as a direct result of hemorrhage. The others of the 34 did die but were considered to have died as a direct result of polio and not as a result of the gastro-intestinal hemorrage. The onset of hemorrhage varied from two days before to 18 days after the onset of paralysis. The average was five days after the onset of paralysis. This, then, is a complication of the acute stage of the disease. In addition to six cases which died as a direct result of hemorrhage, there were two cases in which there was perforation of the duodenum leading to a generalized peritonitis, which was considered to be the cause of death. In the third case, a patient who died of pneumonia was found at post-mortem to have a perforated duodenal lesion.

Of the 34 patients, all but five were over the age of 15. All cases, as previously mentioned, had bulbar involvement. In some cases, there were plastic stomach tubes involved but it seems improbable that this was the cause of ulceration and hemorrhage since similar tubes were used in almost all the patients in the series. There was no evidence that acute viral inflammation of the mucosa of the gastrointestinal tract caused the erosion. Clinical assessment of the degree of anoxia in these acutely ill patients did not impress the authors that this was part of the problem. Because of the previously mentioned implication of shock as the cause of gastrointestinal lesions, it is interesting to note in this report that in 31 of the cases there was no evidence of shock when the hemorrhage was first detected. Further, it is interesting to note that in this report in which the brain lesions responsible were in the brain stem, the hypothesis that brain lesions responsible for gastrointestinal hemorrhage are those of the anterior part of the hypothalamus could not be supported. The authors felt that the question of how the central nervous system involvement leads to gastrointestinal lesions still remains unanswered. In regard to the possibility that the humeral mechanism through the pituitary-adrenal axis, according to the concept of Selye[11] was responsible, it is interesting to note that the authors found histologic changes in the adrenal cortex characteristic of the changes found in sudden stress but these changes were found equally as well in the control group and the group with intestinal lesions alike. This does not rule out sudden stress as the cause of the gastrointestinal hemorrhages but it would appear to mitigate against it as the sole cause.

In the most comprehensive survey of the problem yet published, Dalgaard[12] in 1957 examined 4317 hospital and medical legal post mortems. Of these 385 or 8.9% revealed esophagogastroduodenal ulcerations. Of the 385 cases, 177 appeared to be chronic ulcerations, but 208 were acute ulcerations (4.8%). Of these 208 cases of acute ulcerations only 2 patients did not have evidence of a cerebral lesion or history of severe "functional" cerebral impairment. The 385 cases with esophagogastroduodenal ulceration are listed according to cerebral lesion in the following table:

Table III

Grouping According to Cerebral Lesion or Pathophysiologic Disorder.

Type of Brain Lesion or Pathophysiologic Disorder	Ulceration	
	Acute	Chronic
Traumatic Brain Lesions	35	6
Brain Operations	23	0
Vascular Brain Lesions	67	33
Brain Tumors	15	6
Intracranial Infections	11	0
Intoxications:		
(A) Uremia	12	2
(B) Alcohol	14	6
(C) Barbiturates	4	0
Burns (freezing included)	4	1
Cerebral Hypoxia (Clinical)	9	0
Acute severe stress	15	0
Other cerebral diseases	7	12
No cerebral lesions found	2	71
Brain not examined	0	40
Total	208	177

In further selecting the data, Dalgaard[13] noted that in 117 cases of non-operated cerebral tumors, there were 21 patients with gastrointestinal ulcerations. This is approximately 18% or twice the ulceration incidence of the basic material. Of the 21, 17 were acute ulcerations. This was interpreted as indicative of the presence of neurogenic ulceration.

Dalgaard[12,13] makes several interesting observations. He examined his data carefully and felt that there was no relation to rate of growth of tumors and the nature of the ulcer; that is, rapid growing tumors did not appear to produce predominantly acute ulcerations, nor did slow growing tumors tend to produce predominantly chronic ulceration. It was felt that the neurogenic ulcer etiology was not limited to diencephalic lesions; that is, it was noted that only a few cases involved diencephalic lesions in this series.

DISCUSSION

It would certainly appear from the examination of the data just reviewed that there is reason to accept that intracranial lesions may cause acute ulcerations, perforations and/or hemorrhage of the upper alimentary tract. There are, however, a number of points to consider in this regard.

First, it is recognized that the bulk of the data just reviewed involves autopsy material. It would be far better if the actual problem of acute ulceration, perforation and hemorrhage was based on clinical data with sufficient investigation to support the diagnoses of ulceration, perforation and hemorrhage in association with the cerebral lesions prior to death. However, it is recognized that in most of these cases there was a lack of previous investigation of ulcer and, no doubt, this will be true in general in the future because of the very nature of the problem. When the patient does present with the cerebral difficulty, this illness then most always overshadows the gastrointestinal symptoms if such are present. However, recognition of the possibility of gastrointestinal complications of cerebral disease in the future may lead to significantly improved data in this regard. Investigation of the gastrointestinal symptomatology in such patients with cerebral lesions will be quite difficult, however, because it may be next to impossible for instance to obtain an upper GI series because of the overwhelming cerebral problem. Moreover, by the time an investigation may be done, the gastrointestinal lesion may have already been healed. This, of course, is especially true in children. Also, even should some investigative studies be possible, it would be difficult to time the occurrence of the ulcers because the cerebral symptoms might well over-ride the gastrointestinal symptoms.

The second point of interest is that the original hypothalamic-vagal axis hypothesized by Cushing to be the areas responsible in the brain, when disturbed, for the gastrointestinal complications has now been modified to include higher centers of the brain. Thus it is hypothesized that higher areas of the brain, particularly those areas having to do with the viscera including the uncinate cortex, the amygdaloid nucleus and the claustrum, as pointed out by Papez[14] may exert a balancing effect on hypothalamic areas. When the damping effect of the higher areas is destroyed by a lesion, then the hypothalamic-vagal axis is allowed to function uninhibited and thus might lead to the gastrointestinal ulcer, perforation or hemorrhage.

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CERVICAL INCOMPETENCE

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Cervical incompetence causing pregnancy wastage during the second trimester is characterized by painless dilatation of the cervix and precipitous expulsion of the placenta, membranes, and fetus. The onset is incidious and usually occurs at about 20 weeks gestation. Little concern has been given to this condition until recently because of its relative rarity. It may be one of the most important factors causing habitual abortion in the middle trimester.

To make the diagnosis of an incompetent cervix, certain requisites are necessary. The story of repeated pregnancy losses in the mid trimester must be obtained through a very careful medical history. Sudden loss of amniotic fluid between the 16th and 28th week of gestation without preceding painful contractions is a most significant feature. Theoretically, there seem to be two types of cervical incompetence. Less common than the acquired is the congenital type, occuring in women who have never been pregnant nor have undergone operations related to the cervix. The second type is due to trauma to the cervix, either from delivery or dilatation and curettage of the cervix.

With a history of repeated mid-pregnancy losses, cervical incompetence may be proved by examining the patient at weekly intervals during the critical period. If the cervix painlessly becomes effaced and dilated between the 14th and 28th week it is incompetent. Dilatation is painless and may occur in a week or gradually over a longer period of time. The membranes become palpable, often bulging out to, or beyond the external os. The uterus is usually not irritable, and the membranes can be displaced back into the uterus. The fetus may float down through the cervix within the membranes.

Interest in this condition was aroused during the past year by five patients observed with this difficulty. Four have undergone attempts at surgical correction. Two other cases are reported which were discovered before surgical correction was used.

Case No. 1

L.W., aged 31, gravida 2, para 0, was first observed in 1952. Her first pregnancy ended in a three month spontaneous abortion. At 16 weeks of pregnancy, this patient was seen for the first time in the Out-Patient Department for a prenatal visit. She complained of pressure in the vagina. Examination revealed the membranes presenting almost to the introitus; the cervix was almost completely dilated. Fetal parts could be felt within the sac. Shortly thereafter, contractions began and contents of the uterus were expelled intact. Labor lasted 2½ hours and was essentially painless.

Case No. 2 (Figure 1, 2, and 3)

P.G., aged 36, gravida 5, para 0, when 16 weeks pregnant was admitted to the hospital for observation because of asymptomatic dilatation of the cervix. She was

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Incompetent Cervical Os

Figure 1

This photograph shows the membranes bulging through the dilated cervical os. Although this photograph does not show it, the infant's extremities could be seen floating through the amniotic fluid.

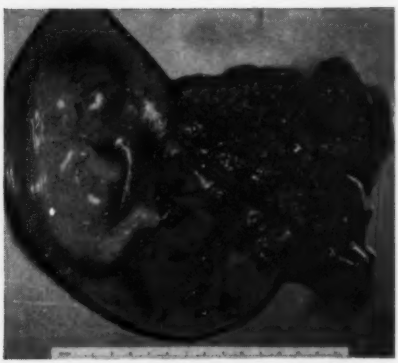

Figure 2

This shows the placenta, intact membranes and fetus after it was expelled from the uterus intact.

Figure 3

This shows the characteristics of the dilated cervical os.

a mild diabetic and was in good control. Her attention was called to her difficulty when she noted a cystic mass bulging through the introitus. On examination the fetal parts were observed actively moving in the amniotic fluid. The following day, without painful contractions, the amniotic sac, placenta and fetus were expelled intact. Bleeding was minimal. Two days later a dilatation and curettage of the uterus was performed. At this time a futile search was made for the cervical defect alleged to be responsible for this condition. Although no defect was detectable, an attempt was made to reduce the caliber of the cervix by placing plicating sutures around its circumference. She delivered her first surviving infant the following year; it weighed four pounds, one ounce.

Case No. 3

N.M., an 18-year old, unwed gravida 1, para 0, was seen for the first time at 27 weeks of pregnancy. She gave a history of having noticed something bulging at the introitus. There were no uterine contractions nor bleeding. On examination, the membranes protruded through a cervix dilated 3-4 cm. This was closed with a purse string of umbilical tape, and the patient was put at bed rest. Examination five days later revealed the cervix again open 5-6 cm. The cervix was reclosed with umbilical tape. She was discharged on the 9th postoperative day. Two weeks later the patient went into labor and delivered a surviving premature female.

Three other patients had cervical repair: two went into labor shortly thereafter and aborted; the other successfully carried to term. One patient aborted before contemplated surgery was performed.

DISCUSSION

Although our experience with this small group of patients has no statistical significance, it is felt that the results are encouraging. With more experience better results should be anticipated.

Most authors feel incompetency usually occurs secondarily to cervical trauma. In Barter's report[1] on 22 patients, all were multigravida. Numerous patients reported by Shirodkar[2] were primagravida. It occurred during the first pregnancy in two of our group. Cervical incompetence does occur in the primagravida, and it is our assumption that this is evidence of a congenital weakness.

Surgical correction on this group was attempted during pregnancy. Shirodkar has operated on both pregnant and non-pregnant patients and has achieved slightly better results in the non-pregnant patient. Lash and Lash[3] reported a method of closure in the non-pregnant state which involved excising a wedge of tissue at the internal os.

Barter[1] uses the purse string operation similar to that described by Shirodkar and feels that this is the most effective of any procedure yet described.

If the patient reaches the last month of pregnancy, most authors feel that cesarean section should be performed. By doing this, the cervix remains intact and future pregnancies may be possible without additional repair. Others think vaginal delivery with immediate repair of the cervix thereafter is adequate.

In cases reported by Barter,[1] patients with completely effaced cervices dilated more than four centimeters invariably had some degree of amnionitis. This was thought to be responsible for uterine irritability eventually causing the patient to abort. Two of the preceding cases fall into this category.

Numerous types of tissue and sutures are being used for closure of the cervix including gut, silk, homologus and heterologus fascia, polyethylene, nylon, dacron and other synthetic products. The synthetic non-absorbable materials are permanent and remain effective if cesarean section is performed.

CONCLUSIONS

The incompetent cervical os appears to be an important cause of mid trimester pregnancy loss. A high index of suspicion based upon history is essential if early diagnosis and prompt effective operative measures are to be accomplished. Although a variety of substances have been used to close the cervix, non-absorbable material appears to be the most satisfactory.

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CLINICAL EVALUATION OF RENAL TUBULAR PHOSPHORUS REABSORPTION TEST

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The diagnosis of hyperparathyroidism continues to be difficult in many borderline cases. Even in far advanced stages of the disease the usual indices of serum calcium, serum inorganic phosphorus and urinary calcium values may be misleading. Since the problem exists, there has been increasing emphasis placed on the urinary excretion of phosphorus as a measure of hyperparathyroidism. The total urinary phosphorus excreted per twetny-four hours is in itself variable and considered of little diagnostic significance.[1] However, various authors have utilized the ratio of reabsorbed to filtered phosphorus and the measurement of per cent tubular reabsorption of phosphorus in the diagnosis of hyperparathyroidism.[2,3] Considerable clinical experience has now been gained with these new techniques.[4]

In the past year we have had the opportunity to evalute the per cent tubular reabsorption of phosphorus (TRP) in 104 patients (Figure 1) while searching for cases of possible hyperparathyroidism. Most of the patients, as might be expected, were studied because of kidney stones or bony demineralization, but patients with other types of metabolic bone disease and renal tubular defects were also included in the study.

The purpose of this report is to add to the total clinical experience of the TRP test and to evaluate its diagnostic usefulness.

METHODS

The control subjects comprised healthy doctors, nurses, and persons undergoing annual routine physical examinations. Patients in the study were taking a diet containing average amounts of calcium and phosphorus and were fasted from midnight on the day of the test. Adequate water intake was given to insure a good urinary flow. Starting at 10 a.m. a four-hour collection of urine was obtained and at 12 noon a blood sample was drawn. Inorganic phosphorus and creatinine determinations were performed on both the blood and urine. From these values the endogenous creatinine clearance was determined and considered to be equal to the glomerular filtration rate. With the knowledge of the serum and urinary phosphorus values the per cent tubular reabsorption of phosphorus was then calculated using the formula $TRP = 1 - \frac{\text{phosphate clearance}}{\text{creatinine clearance.}}$[4] Patients with serum creatinine over 1.3 mg. per cent were not used in the study since the creatinine clearance reflects the glomerular filtration rate only through normal ranges of serum creatinine. Repeat studies in an attempt to eliminate error were carried out on many of the patients. When two or more studies were performed on any one patient the final value used was an average.

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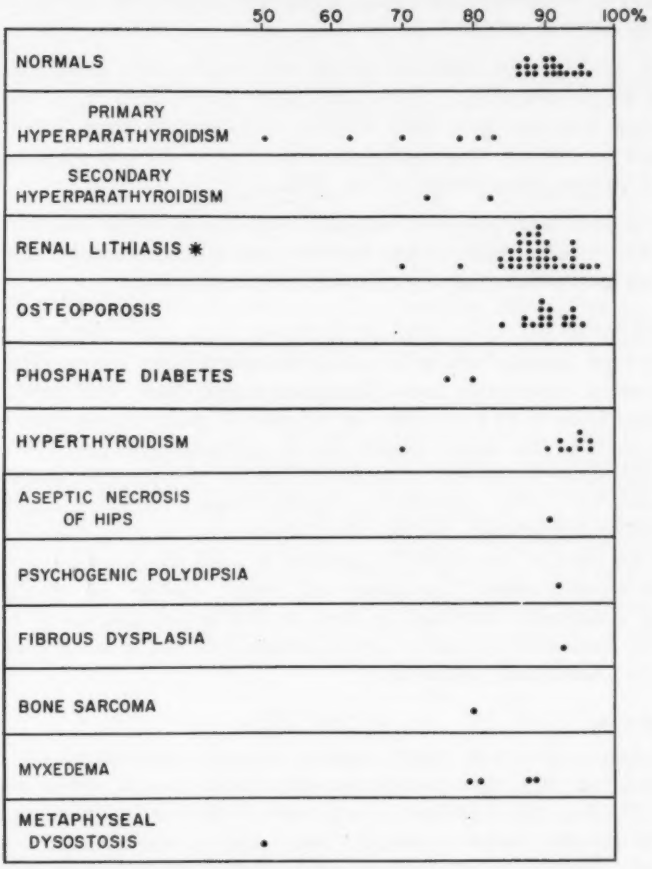

*Not due to Hyperparathyroidism

Figure 1

Comparative values for Phosphorus Reabsorption Test.

RESULTS

1. Normal Subjects.

The TRP in 20 control subjects ranged from 86.9 to 95.1 per cent with a mean of 90.9 per cent. These figures compare favorably with the normal values obtained by others.[3,5]

2. Hyperparathyroidism.

Six patients with surgically proven primary hyperparathyroidism had phosphorus reabsorption tests. The values were reduced in all six instances ranging from 51 to 82 per cent. One patient with surgically proven hyperparathyroidism who had a normal TRP, is excluded because phosphorus had been restricted in the diet pre-

ceding the test. Phosphorus deprivation is known to elevate the TRP in both normal and hyperparathyroid patients.[4]

There was a prompt return to normal after removal of a parathyroid adenoma in five of the patients tested. In the sixth patient despite good initial response after the operation there has been some evidence of progressive renal impairment eight months later as reflected by a rising serum creatinine of 2.8 mg. per cent. This has invalidated progress measurement of the TRP.

Two patients with presumed secondary hyperparathyroidism due to steatorrhea of sprue had reduced TRP of 70.2 and 83.3 per cent respectively. Both of these patients had biochemical and x-ray evidence of osteomalacia.

3. Renal Lithiasis.

Thirty-eight patients with renal lithiasis thought not due to hyperparathyroidism had phosphorus reabsorption tests. The values ranged from 70.2 to 97.1 per cent with a mean value of 89.5 per cent. In only two of these patients however was the value depressed to the degree usually seen in hyperparathyroidism. In one of the patients with renal stones and a depressed TRP to 70.7 per cent there was hypophosphatemia of 2.2 mg. per cent and hypercalciuria. Normal parathyroid glands were identified at operation. In the other patient who has renal lithiasis and a low TRP of 78.6 per cent, parathyroid exploration has not been carried out because the values for serum calcium, phosphorus and urinary calcium are normal. To our knowledge a depressed TRP has not been proved in any instance to be the only biochemical abnormality present in hyperparathyroidism and is not in itself sufficient evidence for parathyroid exploration.

4. Osteoporosis.

Seventeen patients with post-menopausal or senile osteoporosis had phosphorus reabsorption tests. The values ranged from 85 to 95.1 per cent with a mean of 90.9 per cent. The diagnosis of osteoporosis was made on the basis of obvious demineralization of the spine by x-ray in conjunction with a normal serum calcium and inorganic phosphorus. The urinary calcium was either normal or moderately increased.

5. Phosphate Diabetes (Vitamin D — Resistant Osteomalacia).

Two patients with phosphate diabetes had phosphorus reabsorption tests. This disease is considered to be a unifactoral defect in renal tubular reabsorption of phosphorus leading to negative phosphorus balance and osteomalacia. The value was distinctly reduced in both patients to 65 and 80 per cent respectively. The TRP remains depressed in this condition even after forced phosphorus loading has led to healing of the osteomalacia.[6]

6. Hyperthyroidism.

Ten patients with hyperthyroidism had phosphorus reabsorption tests. Previous experimental work in dogs has shown that triiodothyronine reduces the tubular reabsorption of phosphorus. Clinical hyperthyroidism is occasionally associated with hypercalcemia as well as hypercalciuria without associated parathyroid hyperfunction.[8] It therefore seemed worthwhile to evaluate the test in hyperthyroidism. The values

were within normal range in all the tested patients except one. This patient, who had a repeatedly low TRP of 70 per cent, was the only one of the group with associated hypercalcemia to 14 mg. per cent as well as marked hypercalciuria. With the remission of the hyperthyroid state after treatment with I_{131}, the hypercalcemia, hypercalciuria, and TRP all returned to normal range.

7. Miscellaneous.

Single or small groups of patients with a variety of diagnoses were included for one reason or another in the present study. Cases of bilateral aseptic necrosis of the hips, psychogenic polydipsia, and mono-ostotic fibrous dysplasia of bone all had normal TRP. One patient with wide-spread lymphosarcoma of bone had normal serum calcium, phosphorus and creatinine, but a reduced TRP to 78 per cent on one occasion and 82 on another. Four patients with myxedema were tested. Two of these had a normal TRP; but in the other two it was reduced to 79.1 and 81 per cent for which there was no ready explanation.

A remarkable reduction in the TRP to 50 percent was repeatedly found in a 5 year old girl with Metaphyseal Dysostosis.[9] This disease is characterized by a most unusual disorganization of metaphyseal ossification and in addition there is evidence in the few reported cases that hypercalcemia and hypophosphatemia may be present. The x-rays suggested a congenital bone defect, but the chemical changes were characteristic of hyperparathyroidism. Surgical exploration was performed and normal parathyroid glands identified. The striking changes in the serum calcium and phosphorus and the markedly depressed tubular reabsorption of phosphorus were unexplained.

DISCUSSION

There is now sufficient accumulated data to indicate that the measurement of the per cent tubular reabsorption of phosphorus may be of aid in the diagnosis of hyperparathyroidism and certain renal tubular defects. Its final assessment in the evaluation of these conditions, however, awaits further clinical experience with the test. In the opinion of Hills and Burr a normal TRP rules out hyperparathyroidism.[1] Reynolds et al, however, have reported the TRP to be within normal range in some patients with the disease.[10]

The danger of progressive renal failure in hyperparathyroidism, even after its surgical correction, makes the earliest possible diagnosis of paramount importance. The TRP will be a significant additional diagnostic aid if it can be shown to be depressed in hyperparathyroidism before hypercalcemia, hypophosphatemia, and hypercalciuria are present. To our knowledge this has not occurred in any proved case. In our experience the diagnosis of hyperparathyroidism has been well established by diagnostic changes in the serum calcium and phosphorus with the TRP giving only confirmatory evidence. When hyperparathyroidism has progressed to renal failure with elevation of serum creatinine the TRP, like the value for the serum inorganic phosphorus, will be unreliable and misleading. It is probable that the TRP will be useful primarily as supportive diagnostic evidence in hyperparathyroidism. A significantly depressed TRP in the face of borderline charges in serum calcium

and phosphorus or in the urinary calcium, may be sufficient evidence to proceed with parathyroid exploration.

The TRP may be of value in ruling out hyperparathyroidism in cases of renal lithiasis due to other causes. Recently the occurrence of idiopathic hypercalciuria as a factor in the etiology of kidney stones has been more completely described.[11] This condition is characterized by a normal serum calcium level, a low serum phosphorus and an increased urinary calcium excretion. Normal TRP in patients with the above findings is strong supportive evidence that hyperparathyroidism is not causing the lithiasis and unnecessary surgical exploration can be avoided. Of the thirty-eight patients with kidney stones in the present series, eight are considered to have idiopathic hypercalciuria. In seven of these eight patients the TRP was within normal range or only minimally depressed and parathyroid exploration was deferred. The eighth patient, a 48 year old male, had been previously diagnosed at the Massachusetts General Hospital by Dr. Fuller Albright as having idiopathic hypercalciuria. Dr. Oliver Cope carried out parathyroid exploration and found four parathyroid glands grossly and microscopically normal. The patient continued to pass kidney stones and was subsequently seen at the Henry Ford Hospital. Serum calcium was 10.5 and phosphorus 2.2 mg. per cent. Twenty-four hour urine calcium collected while the patient was taking a 150 mg. calcium diet was 211 milligrams. Repeated TRP was depressed to 70 per cent. On the basis of the previous operative findings of four normal parathyroid glands, further surgical exploration of the neck or mediastinum has been deferred, at least for the time. The case illustrates that the TRP in idiopathic hypercalciuria may be significantly depressed either due to renal tubular damage or secondary hyperparathyroidism. It would seem, however, that in most patients with this condition the TRP will be within normal range.

Since most patients with osteoporosis have normal serum calcium and phosphorus, this disorder is readily differentiated from hyperparathyroidism with bone involvement. However, when osteoporosis is rapidly progressive, especially in children, the serum calcium may be elevated.[12] Hypercalciuria occurs frequently in both conditions and is not always a helpful point of differentiation. Depressed serum phosphorus favors hyperparathyroidism, but this important finding may be absent.[4] A normal TRP under these circumstances is substantial evidence against the diagnosis of hyperparathyroidism.

The TRP may be a significant aid in diagnosing renal tubular insufficiency as it occurs in the Fanconi syndrome or in phosphate diabetes. In both of these conditions the renal mechanism for reabsorbing phosphorus is defective owing to an intrinsic alteration in the renal tubule. In the Fanconi syndrome this renal tubular defect for reabsorption of phosphorus is accompanied by similar defects for the reabsorption of glucose and amino-acids. Phosphate diabetes represents the single defect of impaired phosphorus reabsorption.[13]

A depression of TRP alone does not separate an intrinsic renal tubular defect in phosphorus reabsorption from the effect of excess parathyroid hormone. Appreciation of this fact will help avoid errors in diagnosis. As with any other laboratory test, the TRP is of value only when interpreted in light of the other clinical findings.

It should be used only as supportive evidence in the diagnosis of hyperparathyroidism or renal tubular insufficiencies, and final decisions should not be made on basis of the TRP alone.

SUMMARY

1. The results of the per cent tubular reabsorption of phosphorus (TRP) has been evaluated in 104 patients. These have included normal controls and patients with hyperparathyroidism, renal lithiasis, osteoporosis, and intrinsic renal tubular insufficiencies.

2. The TRP may be of acid in the diagnosis of hyperparathyroidism and renal tubular defects, but should be used only as supportive evidence and in light of the total clinical picture.

The authors appreciate the help of Miss MacIntosh, Head Nurse, General Medical Clinic, for her aid in carrying out the phosphorus reabsorption tests.

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THE EFFECT OF MATERNAL HYPOXIA UPON FETAL DENTAL ENAMEL

WILLIAM F. VIA, JR., D.D.S.,* WILLIAM K. ELWOOD, D.D.S.* AND JOSE BEBIN, M.D.**

INTRODUCTION

Hypoxia is considered to be responsible for various disturbances of development originating during or near the termination of gestation. The present study was designed to determine whether hypoxia of pregnant rats will produce disturbances of amelogenesis in their young.

Many experiments have demonstrated the effect of hypoxia on the developing young of various animals. The methods employed to produce oxygen deficiency were dissimilar; and the results of the investigations varied. The methods included subjecting animals to various gas mixtures,[1,3] to simulated altitudes in decompression chambers,[4,9] to geographic areas of high altitude,[10] to hemorrhagic anemia,[11] and ligation of blood vessels.[12,13] Reports of these experiments describe a *decrease* in fertility, number of successful implantations, average litter size, and average weight of the newborn. An increased rate of resorptions, abortions and stillbirths was reported. Living animals born often had malformations of the viscera, vertebrae, ribs, limbs, palate, eyes, cardiovascular system and the central nervous system. The cellular changes related to hypoxic insults have been described by Buchner,[4] Morrison,[14] Windle[12] and others. In some instances the cellular changes may be reversible depending upon the nature of the cells effected and extent of damage.

Little work has been completed concerning the effect of hypoxia upon dental structures. In 1951 Opitz and Lockowandt[15] found no enamel defects in adult rats subjected to periods of hypoxia produced by simulated high altitude.

Ocular malformations, attributed to hypoxia, have been produced by many investigators. Probably the most notable work on prenatal ocular damage was reported by Werthemann and Reiniger[13] in 1950. They subjected pregnant rats to reduced oxygen tension for a 48 hour period at different stages of gastation. The three most common abnormal features of the rat eyes described were: lens degeneration, folded nervous layer of the retina, and thickening of the connective tissue of the vitreous humor.

METHOD

Fifteen Carworth Farms rats with known breeding dates were separated into experimental and control groups. Four of the experimental rats were subjected to hypoxia on the tenth postbreeding day, three on the fifteenth postbreeding day and three on the twentieth postbreeding day. The five control animals were removed from their cages and handled in a like-fashion with the exception that they were not subjected to hypoxia. The pregnant rats comprising the experimental group were placed in bell jars in an atmosphere of 95% nitrogen and 5% carbon dioxide at 730 m.m. Hg pressure and 25° C. until unconscious and apneic. The gas mixture of 95% nitrogen and 5% carbon dioxide was used to produce acute asphyxia of

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short duration, as described by Miller and Miller[16] in 1954. The addition of 5% carbon dioxide to the gas mixture enhanced the possibility of blood pressure elevation due to the action of CO_2 on the vasomotor center and insured the production of acidosis. The asphyxia producing gas mixture was introduced at the rate of three liters per minute through an opening near the base of the bell jar and allowed to exhaust through an opening of the same size at the top of the jar. The test animals were exposed to the gas mixture for 11½ to 14½ minutes, following which they were removed from the bell jar and resuscitated. Experimental and control animals were killed 22 days after breeding.

One rat in each group delivered her young. The other rats were anesthetized and the young were delivered by cesarean section. The ratlets were decapitated and placed in Susa's fixative. The heads of the young were celloidin imbedded and serial sections 12 u. thick were prepared. All sections were saved; every fifth section was stained. Kluver's myelin stain technic was used on selected sections to determine the presence of brain damage. The other sections were stained with hematoxylin and eosin.

RESULTS

The 10 rats in the experimental group delivered 91 living young. Three of the young were dead at birth. The five rats in the control group had forty-two young, two of which were stillborn. None of the ratlets had cleft palates or other gross abnormalities.

No enamel, brain or eye defects were found in any of the control animals. Likewise, none of the animals subjected to hypoxia on the tenth day (Group I) or fifteenth day (Group II) postbreeding had such defects. However, eye and enamel defects were found in some of the animals subjected to hypoxia on the twentieth postbreeding day (Group III).

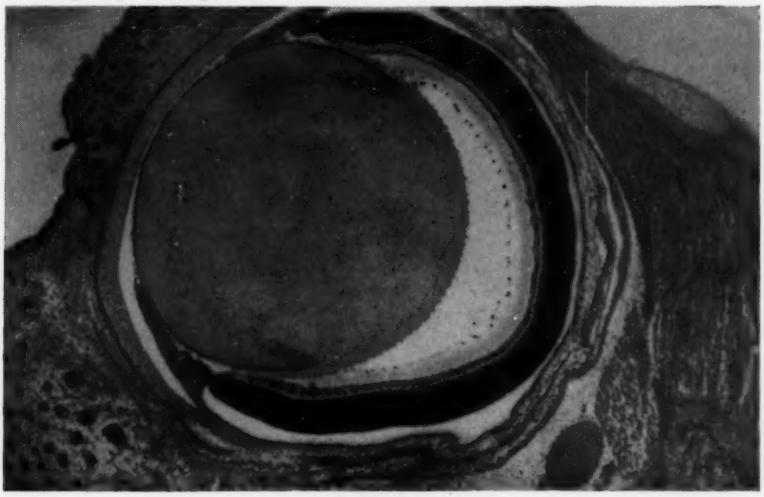

Figure 1

Sagittal section of the eye of a control rat at term.

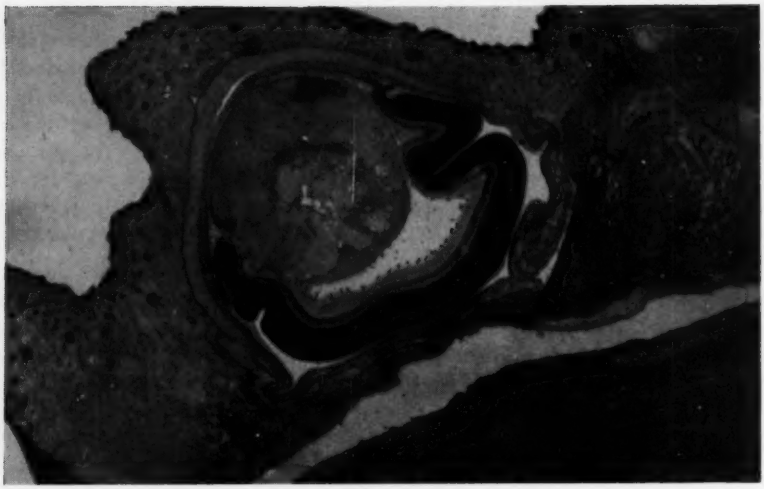

Figure 2

Eye of a ratlet subjected to hypoxia showing degeneration of posterior cell fibers and folded nervous layer of retina.

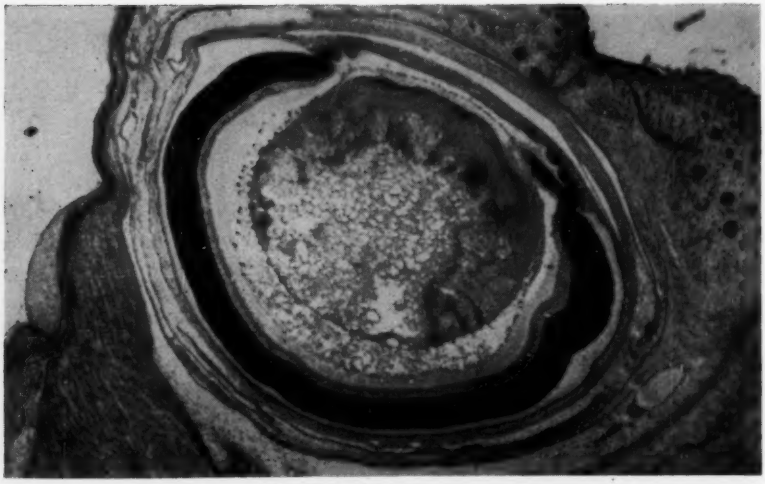

Figure 3

Eye of a ratlet subjected to hypoxia showing extensive lens damage and thickening of the fibers of the vitreous.

Seven ratlets of mothers treated on the twentieth postbreeding day (Group III) had ocular damage. The abnormalities were bilateral and were characterized by degeneration of the posterior lens fibers, folding of the nervous layer of the retina, degeneration of the anterior lens cells, disturbance of the tunica vasculosa lentis and hyaline capsule and a change in the thickness of the fibers of the vitreous.(Fig. 1-3) The ocular defects in these animals are similar to the defects Werthemann and Reiniger[13] attribute to hypoxia.

The lens is particularly susceptible to postmortem changes. To exclude the possibility that postmortem changes caused the observed ocular defects, the eyes of control and experimental animals were compared. Ocular defects were observed only in the asphyxiated animals.

Four ratlets of mothers subjected to hypoxia on the twentieth day of gestation had defects of amelogenesis. The ameloblastic defects were bilateral in two animals, only one incisor was abnormal in each of the others. The defects ranged in width from 60 to 350 microns. In every case, the damage was located near the site at which the deposition of enamel matrix begins. The severity of the observed ameloblastic disturbances ranged from a disorientation and morphologic alteration of ameloblasts, (Fig. 4), to the formation of cystoid areas and abnormal matrix formation, (Fig. 5-7).

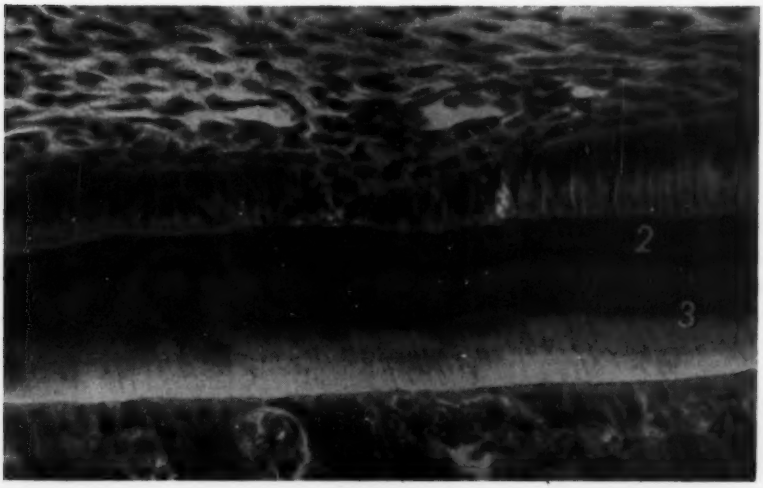

Figure 4

Section of developing mandibular incisor of a ratlet subjected to hypoxia.

1. Ameloblast layer with area of disoriented, pyknotic and morphologically altered cells in center.
2. Enamel matrix.
3. Dentin matrix.
4. Odontoblast layer.

Figure 5

Section of developing maxillary incisor of a ratlet subjected to hypoxia demonstrating a cystoid disturbance of ameloblast layer. Unaffected ameloblasts are seen on either side of damaged area.

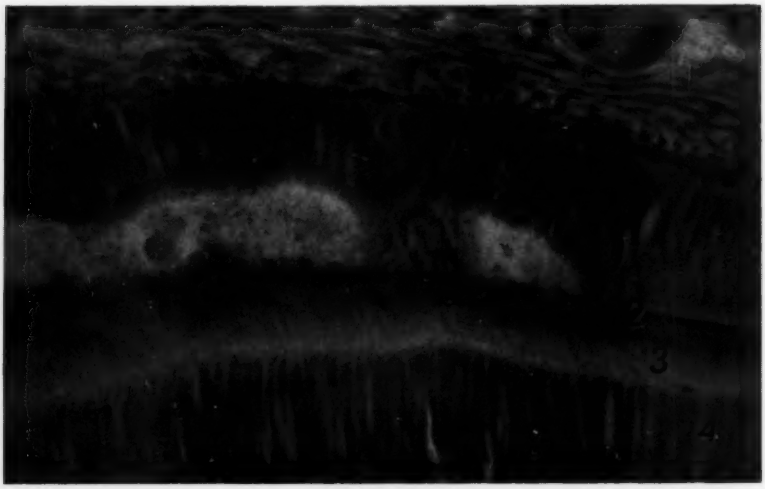

Figure 6

A higher magnification of Figure 5.

1. **Normal ameloblasts — cystoid area to left.**
2. **Dentino-enamel junction.**
3. **Dentin matrix.**
4. **Odontoblast layer.**

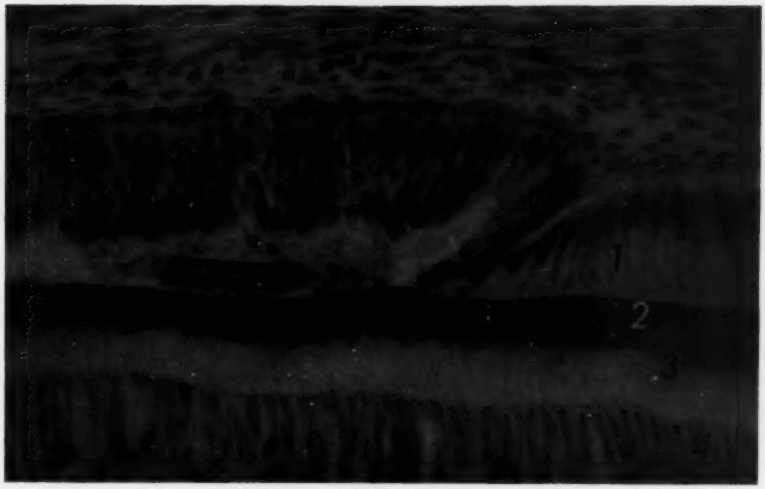

Figure 7

Section of a maxillary incisor of a ratlet subjected to hypoxia.

1. Normal ameloblasts — cystoid area with enamel matrix like globules to left.
2. Dentino-enamel junction.
3. Dentin matrix.
4. Odontoblast layer.

Other specimens of Group III revealed minor distrubances of amelogenesis, only a few cells being affected. These anomalies were not of sufficient magnitude to be considered significant. One animal in the control group also had such a minor abnormality.

DISCUSSION

Ocular and dental defects appeared only in the group of animals subjected to hypoxia on the 20th day of gestation. Since ocular defects due to hypoxia have been reported in younger groups it would appear that the hypoxic insult imposed upon the animals in Groups I and II either was not severe enough to produce defects or the Group III animals were more susceptible to hypoxia, or else an unknown factor caused the defects.

The concurrence of ocular and ameloblastic defects is significant. Eye defects have been attributed to hypoxia by other investigators. Thus, the eye defects may be an indication that the Group III animals did suffer from hypoxia. The disturbances of amelogenesis were found in only one of the litters in this group. This may be explained on the basis of the time when ameloblasts are most sensitive to insult. Tondrey[17] reports the ameloblasts are more easily affected during the appositional stage than at earlier stages. The animals in Group III were subjected to hypoxia on the 20th day of gestation. This date coincides with the beginning of aposition of enamel matrix upon the rat incisor. The litter showing dental defects was born

12 hours before the 22nd day when it was planned to terminate the experiment. The other two litters were delivered by cesarean section on the 22nd day. It is possible, therefore, that enamel matrix formation was progressing at the time the experimental conditions were imposed in the litter exhibiting defects and had not started in other litters.

Our experiments do not demonstrate that any of the observed effects on the developing fetuses were *direct* responses of the ameloblasts to hypoxia. Indirect factors, such as alteration of the acid-base balance and circulatory disturbances, may occur secondarily to oxygen deficiency in both the mother and the developing young. Hypoxia may be only the initiating mechanism. The quantity and quality of these indirect factors accumulating from the translation of the hypoxic treatment of the mother to the response of the fetuses are not understood at present. In addition, the mothers themselves, do not react identically when subjected to the same hypoxic conditions even though they are of the same strain. There is a range of individual variations in structure and function which is characteristic for any strain of rats. The variations in response of the fetal tissues to environmental change must not be ignored. The ameloblastic damage observed in this experiment was either a direct response of ameloblasts to hypoxia or the damage was caused by alterations of metabolism resulting from hypoxia.

SUMMARY

Ten pregnant rats were subjected to an anoxic gas mixture (95% N_2 and 5% CO_2) once during gestation, one group on the 10th day of gestation, a second on the 15th day, and a third on the 20th day. Five other pregnant animals were used as controls.

Defects occurred in only the young of mothers made hypoxic on the 20th day of gestation. There were 19 young delivered to three pregnant rats in this group. Seven ratlets had lens degeneration, four of these had a folded nervous layer of the retina. Four ratlets had disturbances of amelogenesis characterized by abnormal enamel matrix formation and disorientation or degeneration of ameloblasts.

Additional research into the response of dental tissues to hypoxia is in progress.

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HYPOTHALAMIC CONTROL OF THE ADENOHYPOPHYSIS*

JAMES A. ORR, M.D.**

The anterior pituitary gland, adenohypophysis or lobus glandularis, is the portion of the pituitary gland derived from Rathke's pouch of the embryo. It is divided into three parts: The pars tuberalis, the pars intermedia and the pars distalis. (Figure 1).

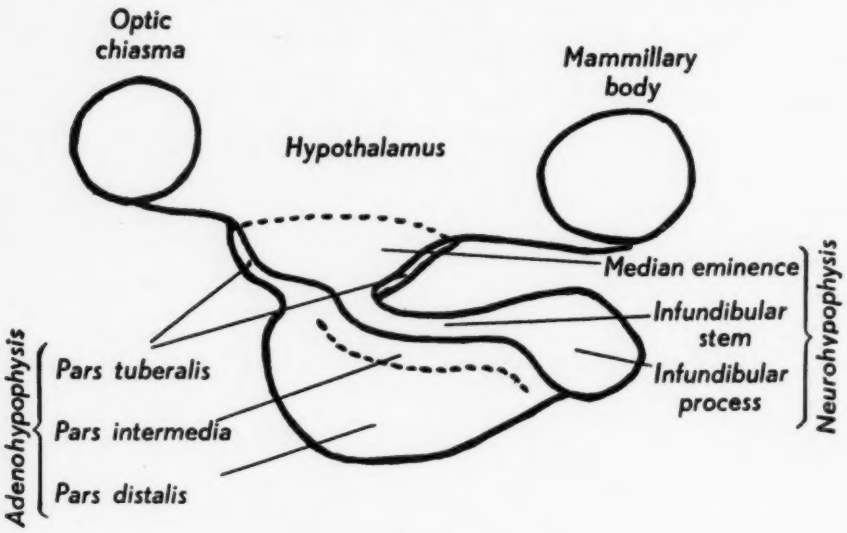

Figure 1

Diagram of a sagittal section through the pituitary gland of a rabbit. (Harris[3])

Over a hundred years ago, Bougery[1] described a nerve supply to the pituitary gland originating from the sympathetic plexus around the carotid artery. Since 1920, when first information concerning hormonal activities of the adenohypophysis was obtained, the nerve supply of this part of the pituitary has been the subject of extensive investigation. It has been suggested that it receives secreto-motor nerve fibers from three sources: sympathetic fibers from the plexus around the internal carotid artery, parasympathetic fibers from the petrosal nerves, and hypothalamic fibers from the median eminence and infundibular stem.

In 1913 Dandy[2] was the first to give a detailed description of the sympathetic pathway to the gland. His findings, as well as that of other workers since that time, have fairly well established that sympathetic nerve fibers pass to the pituitary gland from the surrounding perivascular plexuses, but it is not yet clear whether the main secreting mass of the adenohypophysis, the pars distalis, receives any of these

*Presented December 3, 1958 at the bimonthly Basic Science Seminar.
**Department of Medicine.

fibers, or what the nature of such fibers may be; whether they are secreto-motor or vasomotor. It is very likely that the sympathetic innervation is destined mainly for the pars tuberalis, and that the pars distalis receives few, if any, fibers. This view would indicate that the fibers are vasomotor in nature, for the pars tuberalis is the most vascular region of the pituitary gland, and as far as is known has no definite endocrine function.

It has been shown that complete sympathectomy does not prevent normal reproduction in female cats and does not cause any very significant change in the metabolic rate of cats or rats. These experimental data demonstrate that sympathetic innervation of the pituitary plays no appreciable part in the control of secretion of the gonadotropic and thyrotropic hormones.

Furthermore, there is no sound evidence that parasympathetic innervation of the anterior pituitary gland plays any part in regulating the activity of this gland. It has been shown that removal of the sphenopalatine ganglion does not result in any abnormality of genital development or reproductive capacity in the rat. It has also been demonstrated that the reflex release of gonadotropic hormone which normally follows coitus in the rabbit still occurs after bilateral avulsion of the geniculate ganglion and after the destruction of the petrosal nerves at the geniculate ganglion.

Many workers have noted scanty innervation of the pars intermedia by hypothalamic fibers from the infundibular process. The functional significance of this innervation is unknown since the only hormone known to be secreted by the pars intermedia is the melanophore-expanding hormone. The pars tuberalis also receives fibers from the hypothalamo-hypophysial tract but this highly vascular portion of the gland as far as is known has no definite endocrine function. The majority of workers have either found a complete absence of nerve fiber from the hypothalamic tracts in the pars distalis or the presence of so few that it seems very unlikely that they constitute a secreto-motor innervation for the gland. (Figure 2).

The anterior and posterior hypophysial arteries (a) and (b) are derived from the internal carotid arteries. The arterial twigs (c) to the pars tuberalis plexus are derived from the internal carotid and posterior communicating arteries. The venous drainage (d) passes to surrounding venous sinuses in the dura mater or in the basisphenoid bone. Another vascular system which is found in this region but not shown in this diagram is the hypophysial portal vessels which we will learn later plays a profound role in the hypothalamic control over the adenohypophysis.

The small arterial twigs seen at (c) in Figure 2 run to supply a rich vascular plexus situated in the pars tuberalis of the pituitary gland. From this plexus arises a multitude of capillary loops or tufts which penetrate into the tissue of the median eminence and these come into intimate relationship with the nerve fibers of the supraopticohypophysial, tuberohypophysial and other nerve tracts. These loops or tufts are collectively referred to as the primary plexus of the hypophysial portal vessels. The blood from the primary plexus is drained down the large portal trunks which lie mainly on the anterior or ventral surface of the pituitary stalk. The portal

trunks in turn break up and distribute their blood into the sinusoids of the pars distalis of the adenohypophysis.

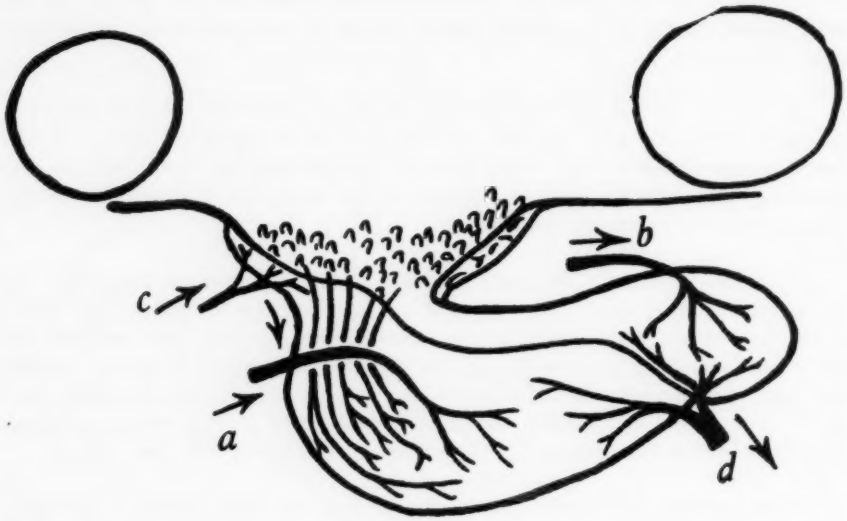

Figure 2
Diagram of a sagittal section through the pituitary gland of a rabbit illustrating the hypophysial blood supply. (Harris[3])

THE REGULATION OF GONADOTROPIC SECRETION

It is well known that changes in the external environment and psychological upsets may influence sexual processes. (Figure 3).

Some examples of exteroceptic factors are as follows:

1. When food is abundant sheep may breed twice a year whereas under-nutrition, if severe enough, may cause disturbance of the estrous and menstrual cycles.

2. The temperature and humidity of the environment seem to play a part in determining the sexual cycle in some forms. The female rat has been found to exhibit lengthened estrous cycles when maintained at low temperatures whereas the normally limited period of testicular activity in the male ground squirrel could be greatly extended by keeping the animals in a constant low temperature.

3. The principal stimulus relating reproductive rhythm to the environmental seasons appears to be light. The ferret is a long-day breeding animal having their breeding season from the middle of March to July or August. The recurrence of estrus in the ferret can be produced by extra illumination. The sheep is a short-day breeding animal which normally breeds from early October to late March. It is

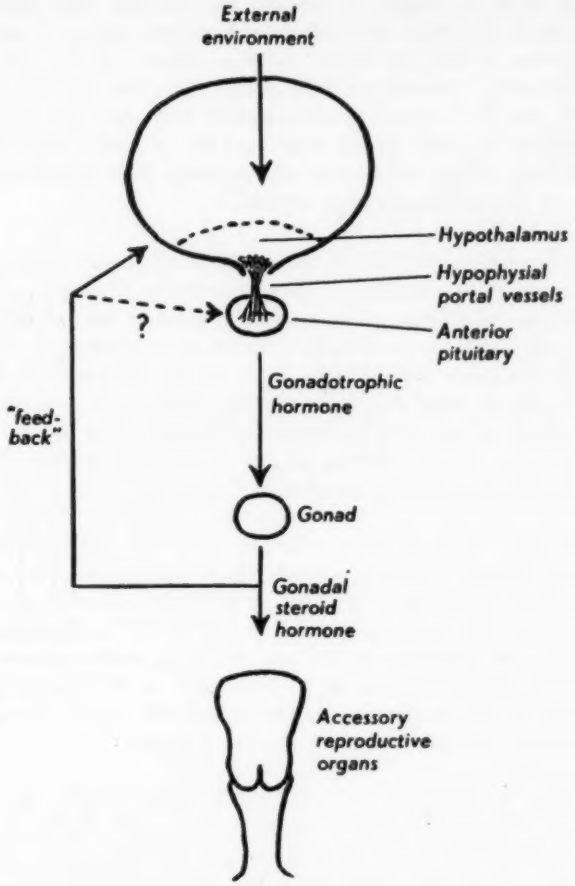

Figure 3

Relationship between the external environment and the reproductive organs. (Harris[3])

found that sheep can be brought into estrus if subjected to a gradually decreasing duration of light each day.

4. The presence of young, eggs, or a companion also play an important role. It is well known that for any one species of bird the number of eggs in a clutch is generally constant within narrow limits. The bird tends to lay a definite number of eggs and brood over them. If eggs are removed one or two at a time, as they are laid, the bird may continue to lay almost indefinitely. For example, a flicker was induced to lay 71 eggs in 73 days in this way.

5. It is well known that changes in the menstrual cycle are often associated with emotional upsets.

The most likely hypothesis to account for the fact that exteroceptive and psychological factors determine and modify the breeding, estrus, and menstrual cycles of so many forms is that the central nervous system controls the secretion of gonadotropic hormone from the pituitary gland. Since the anterior pituitary gland of the embryo, that is, Rathke's pouch, migrates from the roof of the mouth to become attached to the floor of the third ventricle, it would seem likely that the hypothalamus is the part of the central nervous system most directly concerned with the regulation of the anterior pituitary activity.

In 1937 Harris[3] found that stimulation of the tuber cinerum, posterior hypothalamus, or pituitary gland directly might result in ovulation or the formation of cystic or hemorrhagic ovarian follicles. More recently, researchers have shown that electrical stimuli which are ineffective in causing gonadotropic discharge if applied directly to the pituitary gland are fully effective in producing this result if applied to the tuber cinerum. On this basis it is likely that the stimulus from the hypothalamus is transmitted through the pituitary stalk but by structures that are not excitable to electrical stimulation. The component of the stalk which appears to fulfill these requirements is the hypophysial portal vessels.

It has long been known clinically in human beings that hypothalamic lesions may result in genital atrophy. Conclusions from such observations are uncertain since the hypothalamus is anatomically so small in size and consists of such an intricate mass of nerve fibers and scattered cell groups that even a small discrete lesion may affect many functions. Much more significant, however, are the experimental findings that hypothalamic damage may result in disturbance of the estrous cycle, such as persistent estrous in the normally cyclic species and the clinical finding that hypothalamic tumors may produce a state of precocious puberty.

Dey[4] and his collaborators were the first to make a systematic study of the effect of lesions in the hypothalamus or reproductive function. He found that relatively large anterior hypothalamic lesions in the guinea pig were followed by the development of persistent estrous. Lesions which interrupted the connections between the hypothalamus and pituitary resulted in gonadal atrophy whereas lesions directly in the pituitary and lesions in the posterior hypothalamus were without definite effect. Hillarp[5] has found that bilateral lesions placed anterior and ventral to the paraventricular nucleus result in a state of constant estrous. (Figure 4).

The anterior hatched area is the hypothetical location of the "timing center" controlling the cyclic release of gonadotropic substances from the pituitary, as described by Greer.[6] The medial hatched area exerts a modifying influence on the timing center and persistent estrous will result if this area is destroyed.

Since the sympathetic and parasympathetic nervous systems have been shown to have little effect on anterior pituitary activity, the pituitary stalk is the only anatomical pathway by which the hypothalamus can regulate the anterior pituitary secretion.

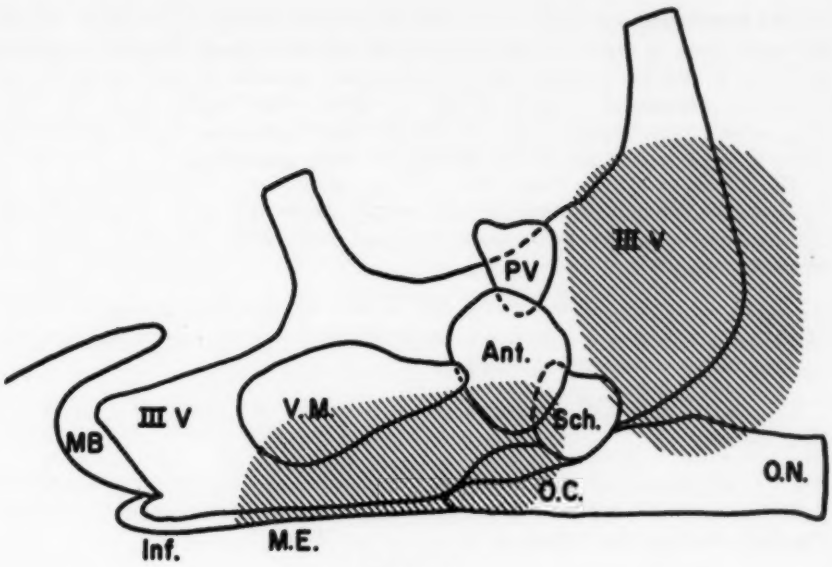

Figure 4

A Diagrammatic Representation of the Rat Hypothalamus. (Greer[4])

ANT = Anterior hypothalamic area.
INF = Infundibulum.
MB = Mammillary bodies.
ME = Median eminence.
OC = Optic chiasm.
ON = Optic nerves.
PV = Paraventricular nucleus.
SCH = Suprachiasmatic nucleus.
VM = Ventromedian nucleus.
III V = Third ventricle.

Many investigators have studied gonadotropic secretion and reproductive activity following cutting the pituitary stalk and observing pituitary function. Very highly discordant results have been obtained. Normal gonadal function has been reported on the one hand and gonadal atrophy has been reported on the other. Some researchers have noted prolonged estrous cycles whereas others have noted normal or absent estrous cycles. As the nerve fibers in the pituitary stalk lack a neurilemmal sheath, they do not regenerate once severed. Most investigators have held one of the following theories concerning the variable results of stalk section: First, it has been suggested that section of the stalk does not necessarily affect the pituitary secretion of gonadotropin; second, that animals which show normal reproductive functions after operation may have had incomplete severance of the stalk.

A possible reconciliation of these variable results became apparent when it was found that the hypophysial portal system of vessels formed a constant anatomical feature of the pituitary stalk and that the flow of blood in these vessels was from the median eminence of the hypothalamus towards the adenhypophysis. Its seems possible that the influence of the hypothalamus on gonadotropic secretion is mediated via these vessels and that the variable results of pituitary stalk section may be explained in terms of variable degrees of portal vessel regeneration across the site of section.

An experiment was carried out in which the pituitary stalk was cut in 19 rats and small plates of paper were inserted between the cut ends of the stalk to prevent regeneration. Eleven of these remained anestrous, gonadal atrophy occurred, and histological examination showed absence of portal vessel regeneration. In eight, irregular or regular estrus cycles recurred and after death some regeneration of the portal vessels was observed around the edge of the misplaced plates.

It is felt that the changes observed could not be due to a reduction in the amount of anterior lobe tissue consequent to a diminished total blood supply for three reasons:

1. Smith[7] in 1932 showed that as little as 10% of the normal amount of anterior pituitary tissue in rats is sufficient to maintain some ovarian activity and that 3% can maintain normal sexual function.

2. The reproductive processes bore no relation to the amount of anterior lobe tissue present.

3. India ink injections showed that the pars distalis was still well vascularized in the animals in which portal vessel regeneration was completely prevented and which remained anestrous after operation.

As stated previously, light stimulation will produce estrus in the ferret. It is believed that this stimulus is mediated by the eyes, optic nerves and probably some nervous reflex pathway ultimately leading to increased pituitary secretion of gonadotropic hormone.

In 1953 Thompson and Zuckerman[8] severed the pituitary stalk in 17 ferrets. They believed that two ferrets, when exposed to light, became estrous even in the absence of any vascular connections between the median eminence and the adenohypophysis. They concluded that the hypophysial portal vessels do not form a part of the pathway by which light stimulates anterior pituitary secretion. In 1954 Donovan and Harris[9] repeated the experiments and obtained different results. He exposed the pituitary stalk of 24 ferrets. In four animals the stalk was left intact, in six, simple stalk section was performed and in 14, the stalk was cut and a paper plate inserted between the hypothalamus and the pituitary gland. After sacrifice, the vascular system was perfused with India ink and celloidin and sections cut serially through the pituitary region. It was found that the appearance of estrous could be correlated with the presence of vascular connections between the median eminence of the tuber cinerum and the anterior pituitary gland. No case of estrous was observed in the absence of such vascular connections.

Another important study concerns the effect of transplantation of the pituitary gland. In 1936 Greep[10] reported that young rats, bearing auto-and homografts of pituitary tissue in the sella turcica showed good anterior pituitary function as evidenced by growth, estrous cycles, pregnancy and lactation. In 1950 and 1952, Harris and Jacobsohn,[11] using hypophysectomized female rats, placed pituitary tissue either under the cut pituitary stalk or a few millimeters laterally under the temporal lobe of the brain where it could become revascularized by the hypophysial portal

vessels. All animals regained a normal estrous rhythm and when placed with normal males, six became pregnant and delivered living young.

It has been noted by many observers, however, that if the anterior pituitary is transplanted into the anterior chamber of the eye or some other area distant from the sella turcica, the functional capacity of the anterior pituitary is markedly reduced. In 1949, Cheng, Sayers, Goodman and Swinyard[12] studied pituitary transplants in hypophysectomized rats and found that the decrease in the weight of the adrenals was in most instances as great as that which occurred in the hypophysectomized animals without grafts. There was also little evidence of secretion of growth hormone or gonadotropic hormone by the transplanted pituitary tissue.

In summarizing the above results, it may be said that there is no evidence that the anterior pituitary gland will maintain normal functions if transplanted to a distant site in the body, and that in this respect the adenohypophysis stands in marked contrast to the ovaries, testes, adrenal cortex, thyroid and parathyroids. However, very different results are obtained if the pituitary gland is removed from the sella turcica so that all vascular and nervous connections are interrupted but is then replaced in the sella turcica or in an adjacent site. Normal anterior pituitary function may then return to such grafted tissue.

ADRENOCORTICOTROPIC SECRETION FROM THE ANTERIOR PITUITARY GLAND.

Adrenocorticotropic Secretion from the Anterior Pituitary Gland.

Although systemic blood levels of adrenalin and of adrenal cortical hormones play a role in the regulation of adrenocorticotropic hormone, we will deal only with the hypothalamic control at this time. The most used indicators for ACTH secretion is the lymphocyte or eosinophil count, or the adrenal ascorbic acid or adrenal cholesterol content. (Figure 5).

As stated previously, pituitary transplants in hypophysectomized animals at a site distant from the sella turcica results in partial or complete atrophy of the adrenal cortex.

In 1950, deGroot and Harris[13] suggested that some neutral mechanism in the hypothalamus is largely responsible for maintaining and regulating the secretion of ACTH. They postulated that hypothalamic nerve fibers liberate some chemical transmitted into the hypophysial portal vessels which is carried to the anterior pituitary gland.

Colfer, deGroot and Harris[14] found that in the rabbit, as in other experimental animals, emotional stress stimuli evoked a lymphopenia. Hypophysectomy abolished this response to stress, though injection of ACTH was still followed by a lymphopenia in the hypophysectomized animal. Electrical stimulation of the posteroir region of the tuber cinerium or mammillary body resulted in a lymphopenia that was similar in time relation and magnitude to that following an emotional stress stimulus or intravenous injection of an appropriate dose of ACTH. Hume[15] in 1953 reported

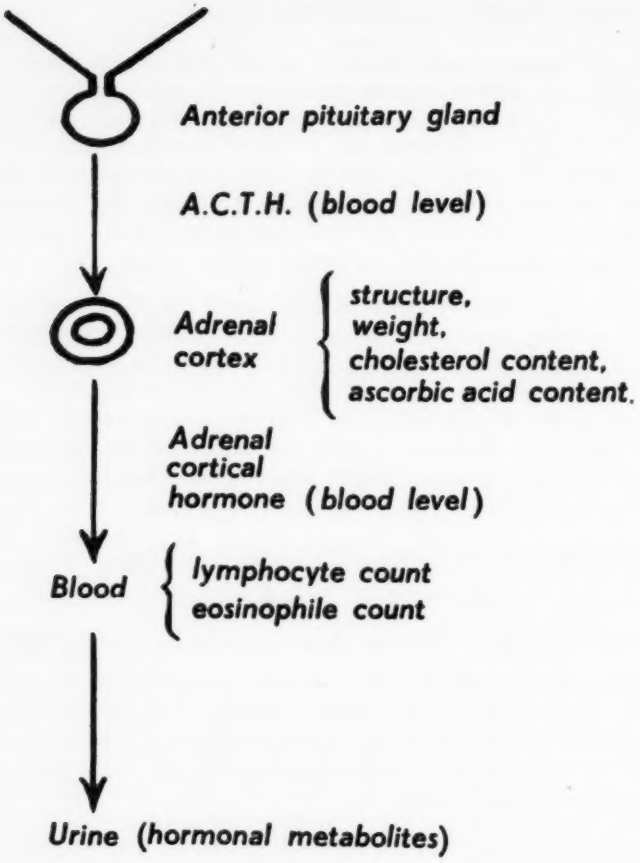

Figure 5

Methods used to measure the activity of the pituitary-adrenal axis. (Harris[3])

that the stimulation of the posterior tuber cinerium of the hypothalamus of dogs also resulted in an eosinopenia.

deGroot[16] in 1952 studied the effect of different types of stress stimuli at varying periods after cutting the pituitary stalk in mice. He found that mice respond to a stress stimulus with a lymphopenia most marked at the third hour after the stimulus. Following simple section of the pituitary stalk, this lymphopenia response was temporarily abolished but was slowly re-established between the 6th and 15th days due to portal vessel regeneration. When a waxed paper plate was placed between the cut ends, the lymphopenic response was abolished for the duration of the experiment. Marked atrophy of the adrenal glands was also noted.

Hume and McCann[17,18] in 1951 and 1953 have found that median eminence lesions in the dog, rat, and cat will interfere with adrenal activation following stress as evidenced by eosinopenia or a decrease in adrenal ascorbic acid content. Other workers have found that the posterior hypothalamus seems to be necessary for adrenal activation in response to stress. (Figure 6).

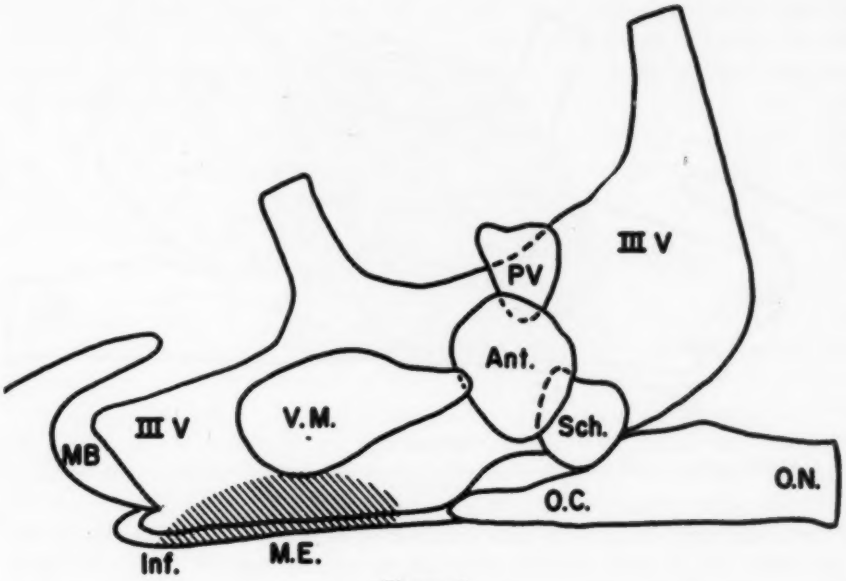

Figure 6

The Hypothalamus of a rat. The hatched section is the primary area controlling corticotropin secretion. (Greer[6])

THYROTROPIC SECRETION OF THE ANTERIOR PITUITARY.

Chronic propylthiouracil treatment in the rat will cause thyroid hypertrophy as well as a tenfold increase in the ability of the gland to concentrate inorganic iodide. By observing the results of hypothalamic lesions Greer found that the area essential for the normal growth response of the thyroid to antithyroid drugs seems to lie in the midline between the paraventricular nucleus and median eminence. Destruction of this area did not alter the ability of the thyroid gland to concentrate inorganic iodine. Lesions responsible for interfering with thyroid iodine metabolism seemed located somewhat posteriorly to those which inhibit the thyroid growth response. The greatest depression of thyroidal iodine metabolism resulted from lesions which prevent goiterogenesis, however. (Figure 7).

In transplanting pituitaries to heterotrophic sites, it was noted that the iodine metabolic factor is relatively unimparied, although the thyroid growth is considerably suppressed. It is therefore believed that the thyrotrophic hormone can be divided into two factors: One, the growth factor; two, the metabolic factor.

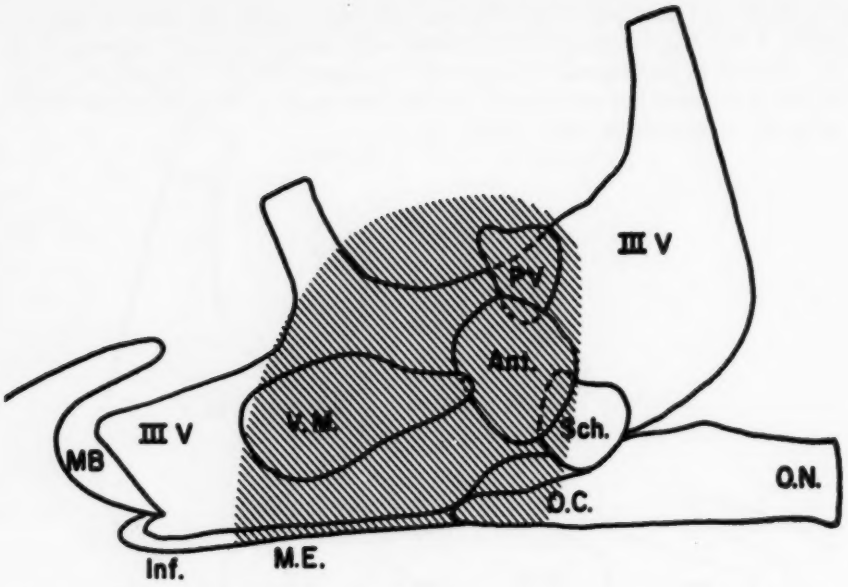

Figure 7

Hypothalamus of a rat. Hatched section is the primary area controlling thyrotropin secretion. (Greer[6])

In summary, evidence has been presented to show that the hypothalamus greatly influences the liberation of hormones from the adenohypophysis. This influence is not mediated through direct neural connections but indirectly through the hypophysial portal vessels.

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ELECTRON MICROSCOPY OF THE FREE BORDER OF THE HUMAN INTESTINAL EPITHELIAL CELL

WILLIAM S. HAUBRICH, M.D.,* JOHN H. L. WATSON, PhD.,**
WILLIAM O'DRISCOLL, M.D.,* AND VIRGINIA VALENTINE**

The particular structure of the free border of the vertebrate intestinal epithelial cell which faces on the lumen of the gut has long tantalized observers employing the ordinary optical microscope. The physiologic significance of the free border is obvious: all nutriment, whatever its form, must pass through it.

Because of optically visible striations, the free border is often referred to as "the striated border" or "the brush border". Such a striated free border is not unique in the intestinal epithelial cell but is seen also in the renal tubule cell which, interestingly, also has to do with absorption.

Over a century ago Henle[1] first described an unusual thickness in the free border ("freie Oberfläche") but he depicted it as structureless. With more discerning study shortly thereafter, began a controversy which lasted more than 100 years until the advent of the electron microscope. Figure 1 shows an optical photomicrograph of normal human jejunal mucosa.

All optical microscopists agreed that fine striations were visible within the free border running perpendicular to the lumenal surface. The controversy concerned whether these striations represented *(a) cilia, or immobile* rods resembling cilia, or *(b)* minute canals or "pores". The history of the controversy has been inclusively chronicled by J. R. Baker.[2] By his own elaborate deductions from optical microscopy, Baker concluded that the striations were minute cylindrical canals. It is interesting (and somewhat disappointing to the present-day reader of Baker's painstaking treatise) that after summing up the arguments, he championed the wrong hypothesis.

In 1949 Barbara Granger and Richard F. Baker[3] first described the electron microscopy of the striated border of the rat intestinal epithelium. The controversy was ended. The striations were clearly shown to be rod-like extensions of cellular cytoplasm. From their measurements of these "microvilli", (average length 0.53μ*, average width 0.75μ), Granger and Baker calculated the surface area of each microvillus to approximate $0.13\ \mu^2$. They further estimated that each cell of the rat epithelium supported about 3000 of these protoplasmic extensions (extrapolating to 200,000,000 per mm^2). As a result of the presence of these microvilli, rather than of plane surfaces, the authors suggested that the entire absorptive surface was increased 30 times.

The microvillous structure of the free striated border has been repeatedly confirmed[4,5,6,7,8] in laboratory animals, chiefly rats and mice. The most elaborate morphologic description and painstaking measurements of fine structure are contained in the monograph by Zetterqvist[9].

*μ (micron) $= 10^{-4}$cm.

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Studying the ultrastructure of the rat intestinal epithelium, Zetterqvist found the length of the microvilli to vary considerably from $0.91 \pm 0.99\mu$, while the width varied somewhat less from $0.10 \pm 0.003\mu$. He observed no inverse relation between varying height and width.

Zetterqvist calculated the surface area of a single whole microvillus to be of the order of $0.283\mu^2$. Further, he counted 47 ± 1 microvilli per μ^2 and estimated the microvillous structure to increase the total surface area of epithelium 14 times.

Coincident with our own studies, Hartman and his associates[10] published the first electron micrograph of human intestinal epithelium. Their brief recording did not specify their observations regarding the free border.

As an extension of our continuing study of the mechanism of fat absorption by the small intestine,[11] we have sought to investigate the ultrastructure of the human intestinal epithelial cell. Our first task has been to obtain satisfactory electron mcirographs of the normal columnar absorbing cell in a fasting state.

MATERIAL AND METHOD

Mucosal biopsies have been obtained from the several segments of small intestine in normal human subjects by means of the Crosby capsule. The interval required for severance of the mucosal specimen, recovery of the capsule, and delivery of the tissue into fixative has been 2 to 4½ minutes in our hands. The time required to retrieve ileal biopsies is slightly longer than for duodenal specimens; the greater period is consumed as the capsule is withdrawn through the pylorus and cardia.

The fixing medium has been isotonic 1 per cent osmium tetroxide buffered to pH 7.4. The fixation period has been varied but is currently 2 hours. The subsequent processing of the tissue for electron microscopy has been modified from the method of Farquhar.[12] A Porter-Blum ultramicrotome was used to cut sections and the micrographs taken with a modified EMU 2B microscope.

OBSERVATIONS

Thus far in the material examined no appreciable differences in the fine structure of the free border have been observed among cells obtained from the duodenum, jejunem, and ileum. However, the study has not been sufficiently detailed or extensive at this juncture to exclude the possibility that fine morphologic differences may exist.

In the electron micrographs, the closely packed, rod-like microvilli which constitute the striated free border have been readily demonstrated. Figure 2 is a schematic representation of the structure of the border as derived from the following electron microscope observations. Along the free margin of single cells, the microvilli are usually of uniform appearance and oriented in the same manner with reference to the plane of the section. The more nearly sagittal is the section of the cell. the more nearly sagittal are the sections of the microvilli. As is readily apparent from Figure 5, the microvilli of one cell may be oriented at angles varying to 90° with reference to those of a neighboring cell. However, often the difference is not so great, and, were it not for the underlying lateral cell membranes, one could not distinguish cell boundaries from the appearance of serial microvilli, Figure 3.

In its sagittal section, Figures 3, 6, 7, each microvillus is a straight or slightly curved rod and its cap is rounded. Among the specimens taken from fasting subjects, each microvillus varies only slightly in diameter through its linear extent and bears an almost indistinguishable resemblance to its immediate neighbors.

It is exceedingly difficult to interpret measurements of the microvilli. Zetterqvist[19] found the diameters of the microvilli to vary but little. In various sections and from different subjects, our observations confirm that the diameters are remarkably constant and average about 0.1 μ. In contrast, the lengths of the microvilli vary considerably. In selected segments our measurements of lengths range from an average of 0.85 μ to an average of 1.60 μ. Not only is this variation observed among speciments from different subjects, which could be attributed to slight differences in post-mortem changes or fixation, but it is apparent within a given segment of epithelium from the same specimen, Figures 4, 6.

This observation, that length varies independently of diameter, suggests that the longer microvilli possess greater whole bulk than the shorter processes. Length is not attained by attentuation of the microvillus itself. The implication is that greater bulk can be derived only from the cytoplasm of the underlying cell. The present methods of electron microscopy make it mandatory that non-living specimens be used, so that it is impossible to observe whether a given microvillus is capable of altering its length and bulk, but such a capability is suggested.

A fine, distinct membrane surrounds each microvillus and is continuous with the plasma membrane of the cell proper, Figures 3, 4, 6. Actually, this limiting membrane is double. In an electron micrograph, such a double membrane manifests itself as two fine lines of increased density separated by an equally thin, lucent space. Although demonstration of the double nature of this membrane in the human is not possible in the half-tones of the present illustrations, it has been observed in the original plates, and the distance between the two has been measured at about 115 A.U.*

The substance of the microvilli appears to be identical with the ground substance of the cytoplasm in the sub-border of the cell itself, Figure 6.

A thin fibrillar structure of irregular width follows approximately the central long axis of each microvillus, Figures 3, 6. Because this fibrillar structure appears to be discontinuous in sagittal sections but is almost always present in transverse sections of the microvilli, it is assumed that it follows a curved or slightly twisting course within the microvillus. In certain sections, this fibrillar structure extends to the distal tip of the microvillus, Figures 3, 4, where it may assume a greater width and density. With varying clarity in certain sections, the fibrillar structure extends below and beyond the base of the microvillus for a distance approximating 1/3 the equivalent length of the microvillus, Figure 4. Such extensions have been designated by other observers as "rootlets". These rootlets are frequently of considerably greater (although irregular) diameter and density than the fibrillar structures within the microvilli. As such, these rootlets probably represent the "subcuticular granules" observed by optical microscopists[2,13].

*A.U. (Angstrom unit) = 10^{-8}cm.

From our current electron micrographs, we have estimated an average of about 49 microvilli per μ^2. Because both the diameter and spacing of the microvilli appear fairly uniform, little appreciable variation in the estimated number of microvilli has been observed over given surface areas in different sections or from different subjects. However, because of the variation in length, noted previously, the multiple to which the presence of microvilli increases the plasma membrane surface of the intestine cannot be conjectured.

SUMMARY

Our observations from electron micrographs of the free border of the human small intestinal mucosa confirm for it the remarkable microvillous structure described by previous investigators working with rats and mice. The ultrastructure of these microvilli has been delineated. From morphologic observations it is suggested that the microvilli are integral and functional components of the columnar epithelial absorbing cell. Precise physiologic correlations with submicroscopic anatomy are not apparent. Studies directed toward elucidating possible morphologic changes in the microvilli under varying physiologic conditions and in disease are continuing.

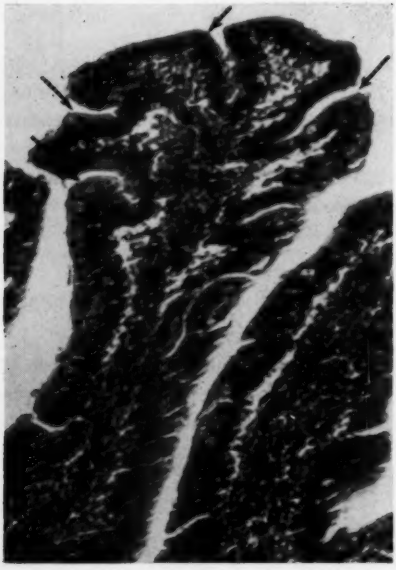

Figure 1

Photomicrograph of normal human jejunal mucosa as viewed through ordinary optical microscope at a magnification of about 270x. Arrows indicate the striated border along the free margin of the simple columnar epithelium. Fine perpendicular striations known to be present cannot be discerned in the half-tone reproduction.

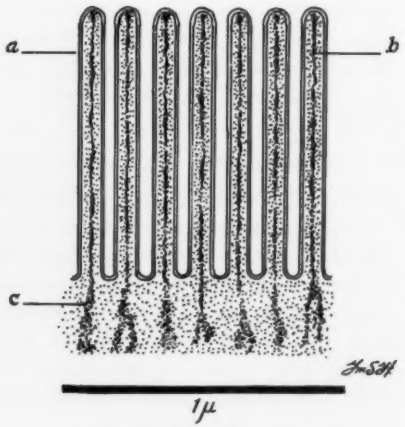

Figure 2

Schematic drawing of the rod-like cytoplasmic projections (microvilli) which compose the free border of the intestinal epithelial cell: (*a*) continuous paired plasma membrane, (*b*) fibrillar structure which extends below the base of the microvillus to form (*c*) the rootlet. The figure is drawn to scale representing a magnification of 42,000x.

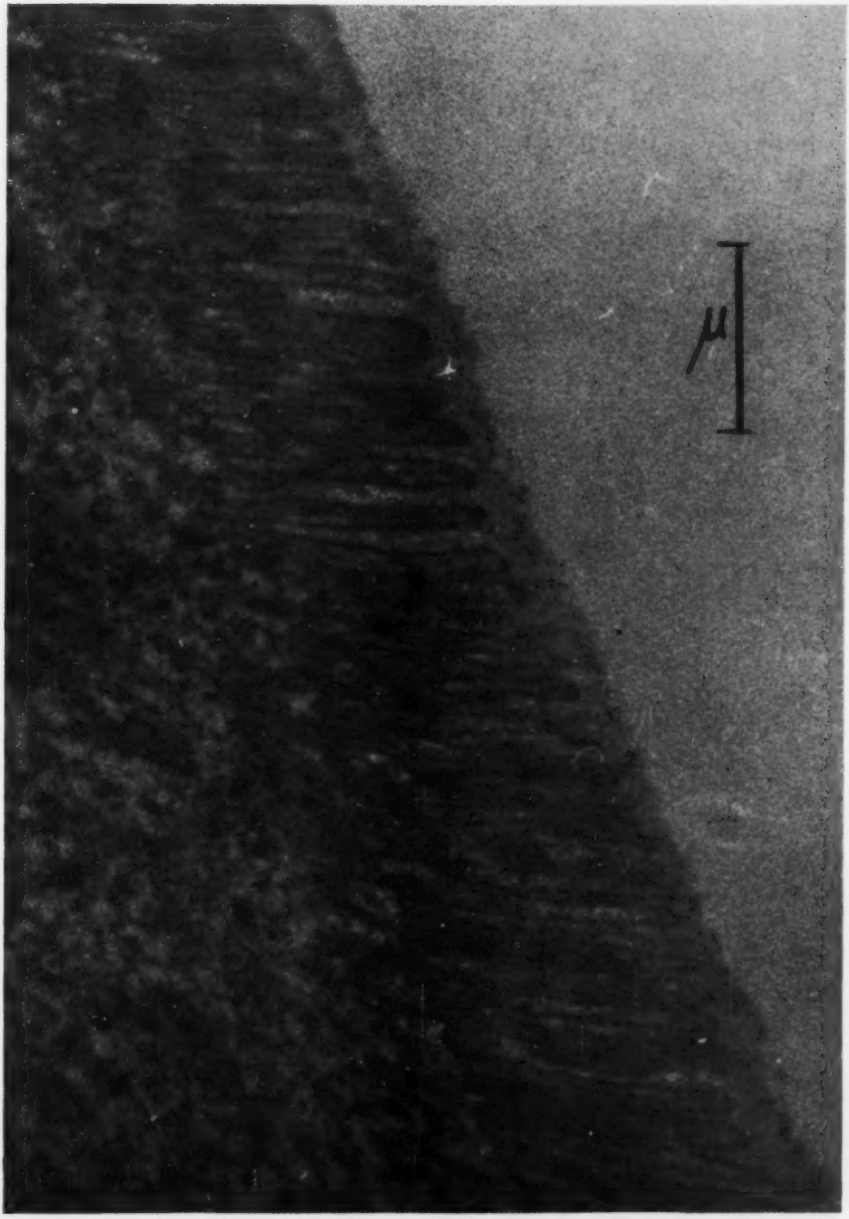

Figure 3 x28,000

Electron micrographs of tissue sections prepared from capsule biopsies of normal human jejunal mucosa, illustrating the fine structure of the striated border. Figures 3 and 4 are from the same subject; Figures 5, 6, and 7 are from a different subject. See text for detailed description.

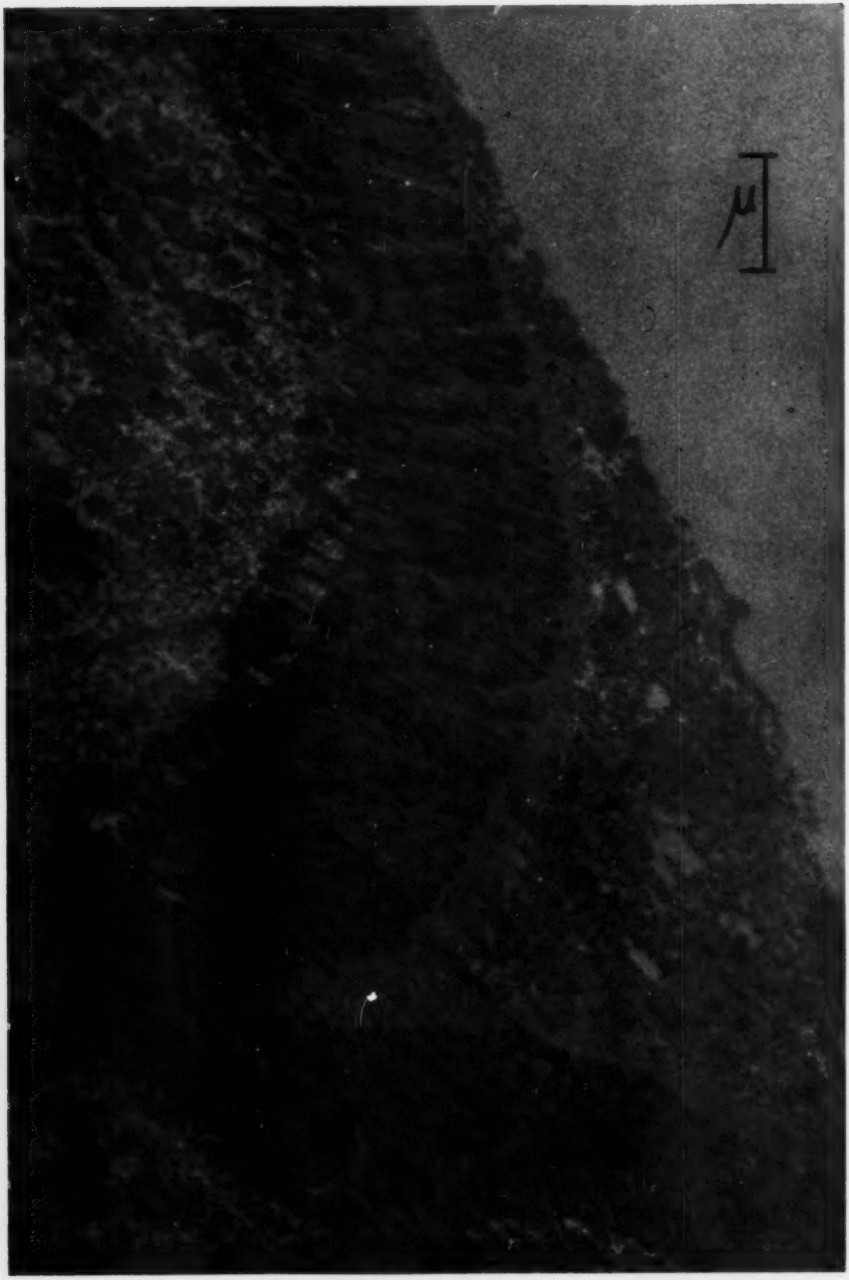

Figure 4 x17,000

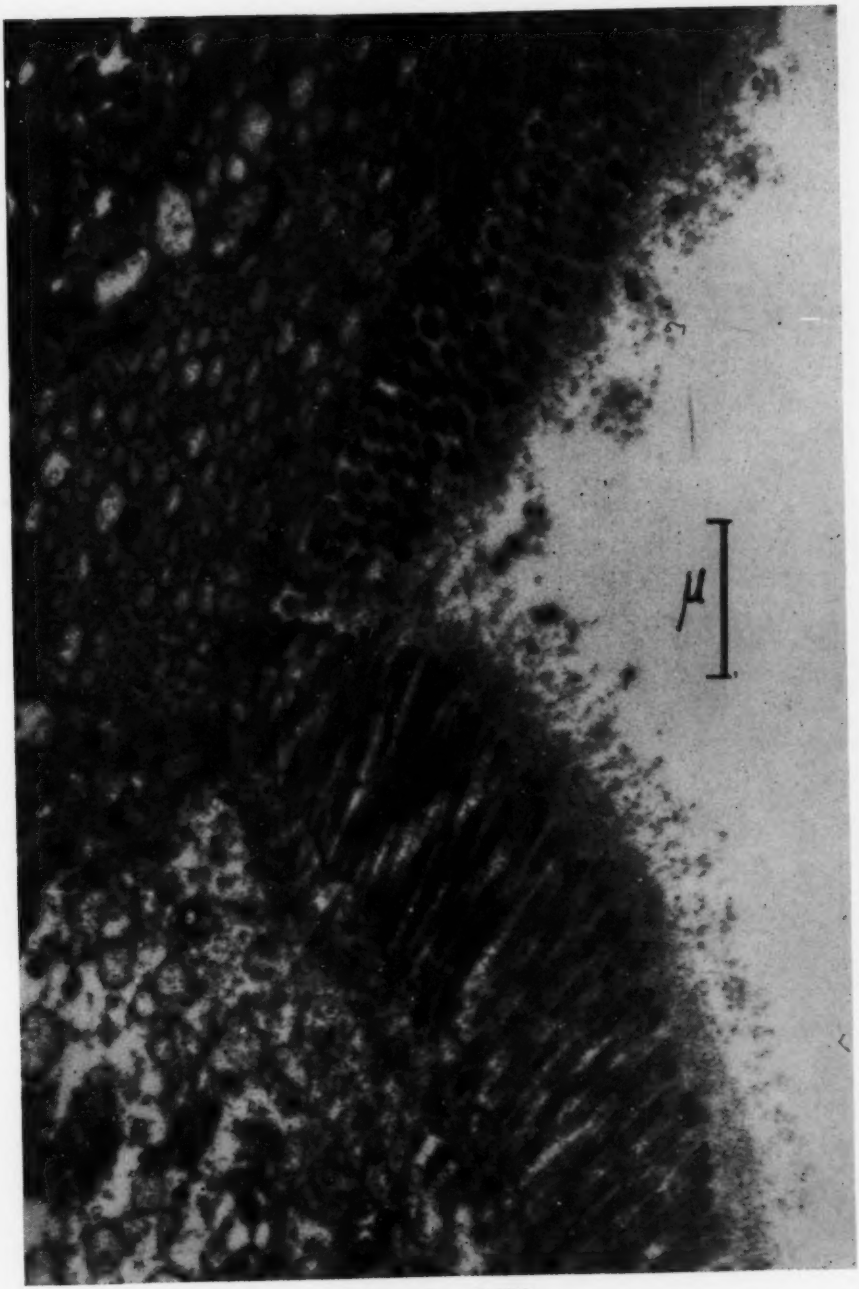

Figure 5 x23,000

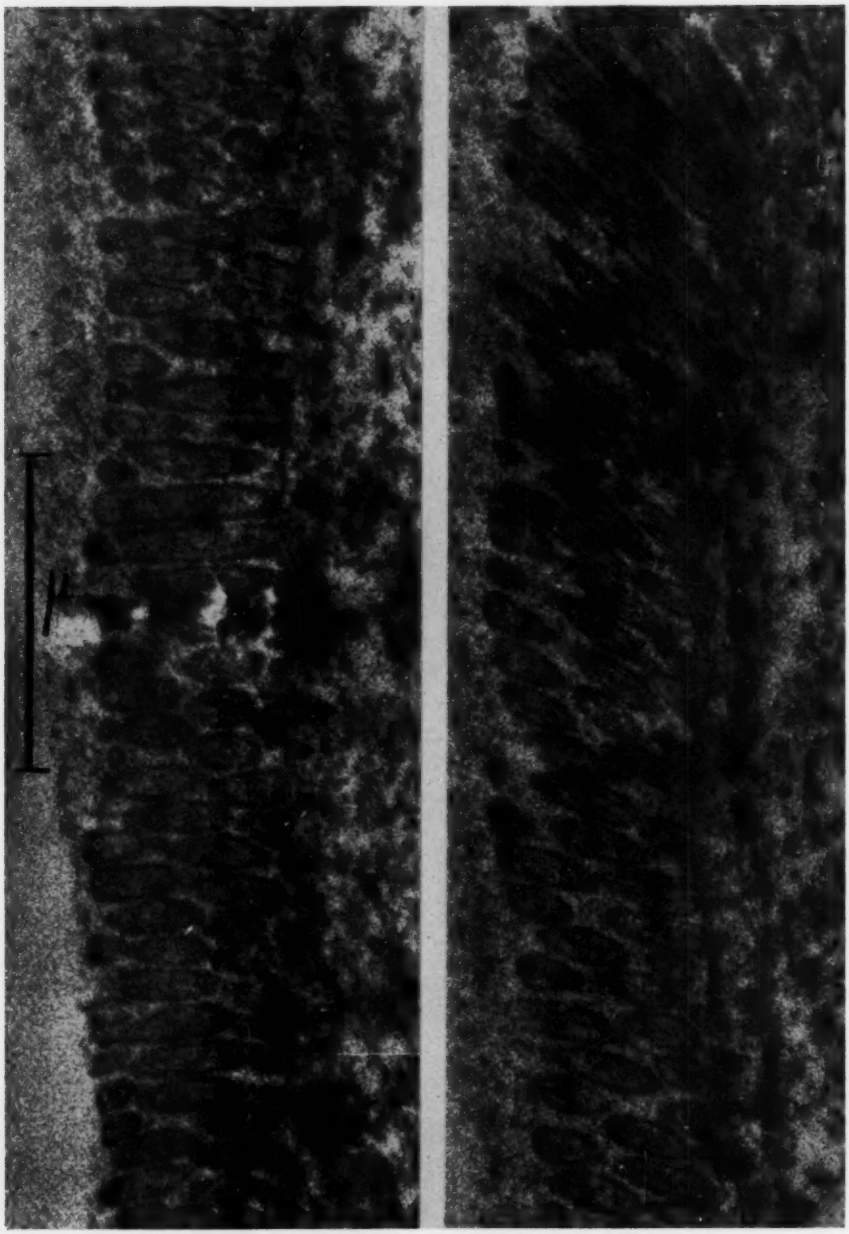

Figure 6 x48,000

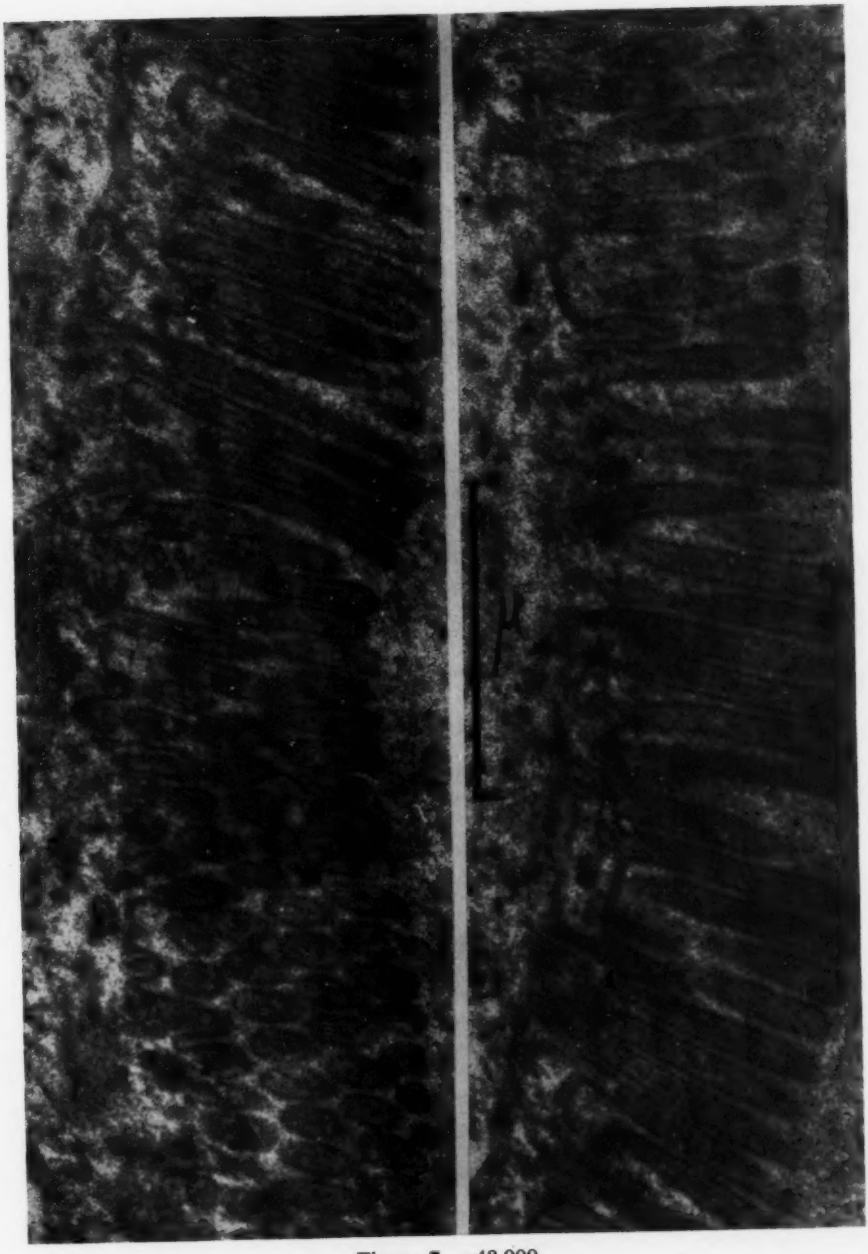

Figure 7 x48,000

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INTRODUCTION OF NEW STAFF MEMBERS

THOMAS R. NEBLETT, PhD., joined the staff September 1957 in the Laboratory Department, division of microbiology. His home is Detroit and he was born June 4, 1928. Dr. Neblett received his B.S. degree from Michigan State in 1951 and his PhD in Microbiology and Public Health from the same University in 1957. His Master's degree was from Wayne University, 1953. During this time, he worked on the biologic activity of lipids derived from enteric bacteria and their characterization by infrared spectrometry. He was a predoctoral fellow in the New England Institute for Medical Research during 1954 and 1955. He also did graduate work in cell chemistry at Columbia University, New York. He belongs to the Society of American Bacteriologists, the American Association for Advancement of Science and Sigma Xi. He is unmarried and lives at 14294 Mark Twain Street, Detroit, Michigan.

JOHN E. SHICK, M.D., became a member of the staff of the Department of Radiology October 14, 1957. His home is Chicago, Illinois and he was born February 24, 1926. He gained his A.B. degree from Harvard University in 1947 and M.D. degree from Northwestern in 1951. He spent his internship at St. Luke's Hospital in Chicago and radiology residency at Jefferson Medical College in Philadelphia from 1954 to 1955 and at Barnes Hospital in St. Louis from 1955 to 1957. Dr. Shick was officer-in-charge of the Dispensary Radiology Department while serving in the Navy from 1952 to 1954 at Bainbridge, Maryland. He is certified by the American Board of Radiology and belongs to the American College of Radiology. He lives with his wife and two children at 15902 Artesian, Detroit 23, Michigan.

CAMPBELL WHITE, M.D., joined the Henry Ford Hospital Orthopedic staff January 1, 1958. He was born November 29, 1923 and his home is in Sudbury, Ontario. He received his M.D. degree from the University of Toronto in 1950. From 1942 to 1945 he served as a pilot in the Royal Canadian and Royal Air Force. After an internship at St. Joseph's Hospital in Toronto, he was resident in general surgery at the Royal Victoria Hospital in Montreal. He had orthopedic training there as well, and at Montreal Children's Hospital and the Shriners' Hospital for Crippled Children. Then Dr. White was an orthopedic registrar at Princess Elizabeth Orthopedic Hospital, Exeter, England and at St. Bartholomews, London. He spent his last year in residency at Queen Mary Veterans' Hospital, Montreal. He is a member of the Canadian Orthopedic Association and is certified by the Royal College of Physicians and Surgeons of Canada in Orthopedic Surgery. He is married and has two children. His present address is 466 Calvin Street, Grosse Pointe Farms.

ANDREAS MARCOTTY, M.D., is a member of the Department of Neurology and Psychiatry, having joined the staff March 1, 1958. He was born May 23, 1923 in Duesseldorf, Germany. In October 1948 he received his M.D. degree from the University of Freiberg. He spent his internship in Neurology and Psychiatry at the Freiberg University Hospital. He then had one year in child psychiatry in the University Hospital at Waldau-Berne, Switzerland and two years in the psychiatric clinic at Kuesnacht-Zuerich. Dr. Marcotty was also resident in Psychiatry at the Butler Hospital in Providence, Rhode Island and chief resident in Psychiatry at the Boston City

Hospital. He spent two years in the U. S. Army as chief of the NeuroPsychiatric service at Fort Riley, Kansas. Before coming to the Henry Ford Hospital he was an Assistant in Psychiatry at Harvard Medical School. He is married with four children and lives at 1849 Orchard Lane in Bloomfield Hills, Michigan.

ROBERT S. ORMOND, M.D., jointed the staff of the Department of Radiology on July 1, 1958. He was born in Detroit, January 1, 1923. In 1944, he obtained the A.B. degree from Princeton University and the M.D. degree from the University of Pennsylvania in 1947. Dr. Ormond interned at the Henry Ford Hospital, then was resident in Pathology at the Wayne County General Hospital during 1949 and 1950. He was in the U. S. Navy the next two years as chief of Pathology at the 4002 U. S. Army Hospital in Fort Smith, Arkansas. He was also assistant in Dermatology at Santa Marguerita Hospital, Camp Pendleton, California. From 1952 to 1955, he was resident in Radiology at Henry Ford Hospital. He was also in private practice doing Radiology in Dearborn. Dr. Ormond is certified by the American College of Radiology, the Radiologic Society of North America and the Detroit Roentgen Ray Society. He is married, has five children, and lives at 9039 Annapolis Street, Detroit, Michigan.

IRVING O. DEIN, M.D., became a member of the Department of Neurology, November 1, 1958. He was born January 9, 1915 in Atlantic City. Dr. Dein received his A.B. degree from Duke University in 1936 and M.D. degree from the University of Louisville, Kentucky in 1940. He interned at Welfare Hospital in New York in the Columbia Division. After a year as Neurology resident there, he joined the U. S. Third Army for 3½ years as Medical Commander of a collecting company. He then spent a two years' residency in internal medicine at the V. A. Hospital in Louisville, followed by a year in Psychiatry. He then joined the staff in Neurology. Dr. Dein was chief of the Neurology Service at the V. A. in Louisville from 1951 to 1956. During 1956 he also did part time practice. In 1957 he was assistant professor of Neurology at the University of Louisville Medical School. He belongs to the American Academy of Neurology and was certified by the American Board of Psychiatry and Neurology in 1951. He has also been an examiner for the American Board of Psychiatry and Neurology in Neurology. He lives at 14126 Inkster Road in Detroit and is married with four children.

WILLIAM J. BUTLER, M.D., joined the Department of Urology, January 1, 1959. His home is in Chicago and he was born September 17, 1918. He received his B.S. degree from the University of Illinois in 1939 and his M.D. degree in 1941. He interned at the University Hospital in Ann Arbor. The next three years, he was with the U. S. Army 9th Infantry Medical Corps. He was resident in Surgery at the University Hospital 1945-1946 and Urologic resident 1946-1949, receiving the M.S. degree in Surgery from Michigan in 1949. He has been in private practice in Urology at St. Joseph, Michigan. Dr. Butler is certified by the American Board of Urology and is a fellow of the American College of Surgeons. He belongs to the North Central Section of the American Urologic Society. He lives at 165 Overhill Road in Birmingham with his wife and two children.

INTERNATIONAL SYMPOSIUM
THE BIOLOGY OF PYELONEPHRITIS

October 8, 9, 10, 1959

The professional staff of the Henry Ford Hospital with the initial advice and support of the Board of Trustees and Dr. Robin C. Buerki, Executive Director, of the Henry Ford Hosiptal, is sponsoring an international symposium on the subject The Biology of Pyelonephritis. This symposium will be held at the Henry Ford Hospital, October 8, 9, 10, 1959, in the Clinic Auditorium. The preliminary program follows and has been prepared with the help of the advisory members:

PROGRAM COMMITTEE

ADVISORY MEMBERS:

Chairman

Edward H. Kass	Associate Professor of Bacteriology and Immunology, Harvard Medical School.
Paul B. Beeson	Ensign Professor of Medicine, Yale Univ. School of Medicine.
Maxwell Finland	Associate Professor of Medicine, Harvard Medical School.
George Gee Jackson	Associate Professor of Medicine, University of Illinois College of Medicine.
Gilbert H. Mudge	Professor of Pharmacology & Experimental Therapeutics School of Medicine, Johns Hopkins University.
Reed M. Nesbit	Professor of Surgery, University of Michigan Medical School.

LOCAL MEMBERS:

Chairman

Edward L. Quinn	Division of Infectious Diseases, Henry Ford Hospital.

Secretary

Robert C. Horn, Jr.	Department of Laboratories, Henry Ford Hospital.
A. Waite Bohne	Division of Urology, Henry Ford Hospital
James M. Colville	Division of Infectious Diseases, Henry Ford Hospital.

International Symposium

PROGRAM

First Morning Session — Thursday, October 8, 1959

9:00 A.M. Remarks of Welcome

Robin C. Buerki, Executive Director, Henry Ford Hospital

PATHOGENESIS OF PYELONEPHRITIS

Chairman: *Paul B. Beeson,* Yale University, New Haven

9:10 Bacteriology and Pathogenesis of Pyelonephritis
R. H. Gorrill, Guy's Hospital Medical School, London, England

9:30 Observations on the Pathogenesis of Chronic Nonobstructive Urinary Tract Infection in the Rat
Lucien B. Guze, Veterans Administration Center, Los Angeles, Calif.

9:40 Ascending Pyelonephritis Consequent to the Production of Bacteriuria in the Rat
Ennio C. Vivaldi, Boston City Hospital, Boston, Massachusetts

9:50 The Course of Experimental Retrograde Infection of the Nonobstructed Urinary Tract
William R. McCabe, University of Illinois, Chicago, Illinois

10:00 General Discission

10:15 Intermission

10:40 Relationship of Renal Toxicity of Drugs to Pyelonephritis
Hans U. Zollinger, Institute of Pathology, St. Gallen, Switzerland

11:00 The Role of Bacterial Enzymes in the Pathogenesis of Pyelonephritis
Abraham I. Braude, University of Pittsburgh, Pittsburgh, Pa.

11:20 Obstruction in the Etiology of Pyelonephritis
David M. Davis, Haverford, Pennsylvania

11:40 Discussion Designated
Herbert S. Talbot, Veterans Administration Hospital, West Roxbury, Massachusetts

11:45 General Discussion

12:15 Summation
Paul B. Beeson, Yale University, New Haven, Conn.

12:30 Luncheon

Biology of Pyelonephritis

First Afternoon Session — Thursday, October 8, 1959

STRUCTURE AND FUNCTION OF THE KIDNEY

Chairman: *Gilbert H. Mudge,* Johns Hopkins University, Baltimore

2:00 P.M. Cytochemical and Electron Microscopic Studies of the Rat Kidney
Alex B. Novikoff, Albert Einstein College of Medicine, N. Y., N. Y.

2:30 Discussion Designated
Robert M. Kark, University of Illinois, Chicago, Illinois

2:40 General Discussion

3:00 Intermission

3:15 A General Survey of Localization of Function Within the Nephron
Robert W. Berliner, National Heart Institute, Bethesda, Maryland

3:35 Morphologic Expression of Functional Changes in the Normal Nephron
E. M. Darmady, Central Laboratory, Portsmouth, England

3:55 Morphologic Expression of Functional Changes in the Abnormal Nephron
Jean Oliver, The Renal Research Unit, Summit, New Jersey

4:15 Intrarenal Pressures
Carl W. Gottschalk, University of North Carolina, Chapel Hill, N. C.

4:35 Pyelovenous Communications
Rafael Dominguez, St. Luke's Hospital, Cleveland, Ohio

4:45 General Discussion

5:15 Summation
Gilbert H. Mudge, Johns Hopkins University, Baltimore, Maryland

First Evening Session — Thursday, October 8, 1959

THE RENAL LESION IN PYELONEPHRITIS

Chairman: *Robert C. Horn,* Henry Ford Hospital, Detroit

8:00 P.M. Significance and Specificity of the Renal Lesion in Pyelonephritis
Paul Kimmelstiel, Milwaukee County Hospital, Milwaukee, Wisconsin

8:20 Recognition of Pyelonephritis in Renal Biopsies
Claus Brun, Central Clinical Laboratory, Copenhagen, Denmark

8:40 Discussion Designated
Conrad L. Pirani, University of Illinois, Chicago, Illinois

8:50 Evolution of the Experimentally Produced Pyelonephritis Lesion
Robert H. Heptinstall, St. Mary's Hospital, London, England

9:10 Hereditary Chronic Nephritis
Gerald T. Perkoff, Universary of Utah, Salt Lake City, Utah

9:20 General Discussion

Second Morning Session — Friday, October 9, 1959

FUNCTIONAL DISTURBANCES ASSOCIATED WITH PYELONEPHRITIS

Chairman: *Louis G. Welt,* University of North Carolina, Chapel Hill

9:00 A.M. Mechanism of Urinary Acidification
Robert F. Pitts, Cornell University Medical College, New York, N. Y.

9:20 Concentrating Mechanisms in the Kidney
Heinrich Wirz, University of Basel, Basel, Switzerland

9:40 The Pathology of the Medulla in Relationship to Loss of Concentrating Power in Some Experimental and Clinical Diseases of the Kidney
Franklin H. Epstein, Yale University, New Haven, Connecticut

9:50 General Discussion

10:25 Intermission

10:40 Early Evidence of Renal Dysfunction in Pyelonephritis with some Remarks on the Pathogenesis of the Pyelonephritic Contracted Kidney
Jan Brod, Institute for Cardiovascular Research, Prague, Cezch.

11:00 Early Evidence of Renal Dysfunction in Pyelonephritis
Neal S. Bricker, Washington University, St. Louis, Missouri

11:10 Acute Urinary Tract Infection — A Long-Term Study
Lawrence R. Freedman, Yale University, New Haven, Connecticut

11:20 Some Clinical Aspects of Chronic Pyelonephritis
Aronld S. Relman, Boston University, Boston, Massachusetts

11:30 General Discussion

12:05 Summation
Louis G. Welt, University of North Carolina, Chapel Hill, N. C.

12:30 Luncheon

Second Afternoon Session — Friday, October 9, 1959

THE MICROFLORA IN PYELONEPHRITIS

Chairman: *George G. Jackson,* University of Illinois, Chicago

2:00 P.M. Chairman's Remarks

2:10 Taxonomy of the Various Groups of Enteric Bacteria
Philip R. Edwards, Communicable Disease Center, Chamblee, Georgia

2:30 Discussion Designated
Erwin Neter, Children's Hospital, Buffalo, New York

2:40 The Bacterial Flora of the Urinary Tract
Ellard M. Yow, Baylor University, Houston, Texas

3:00 P.M. The Role of Asymptomatic Bacteriuria in the Natural History of Pyelonephritis
Edward H. Kass, Harvard Medical School, Boston, Massachusetts

3:20 Bacteriuria — The Incidence in 5000 Cases Studied
William Schwartz, Tufts University, Boston, Massachusetts

3:30 Natural Inhibitors of Bacterial Multiplication
Derrick Rowley, St. Mary's Hospital Medical School, London, England

3:50 The Role of Natural Inhibitors in the Mechanisms of Localization of Bacteria in the Kidney
Paul B. Beeson, Yale University, New Haven, Connecticut

4:00 Intermission

4:15 The Lymphatics and their Relationship to Infection
John J. Murphy, University of Pennsylvania, Philadelphia, Penn.

4:25 The Relationship of Instrumentation to Infection
Reed M. Nesbit, University of Michigan, Ann Arbor, Michigan

4:35 General Discussion

5:05 Summation
George G. Jackson, University of Illinois, Chicago, Illinois

Second Evening Session — Hotel Statler — Friday, October 9, 1959

6:30 Reception

7:30 Banquet Address
Maurice B. Strauss, Veterans Administration Hospital, Boston, Mass.

Third Morning Session — Saturday, October 10, 1959

RELATIONSHIP OF PYELONEPHRITIS TO OTHER CLINICAL STATES

Chairman: *Maurice B. Strauss,* Veterans Administration Hospital, Boston

9:00 A.M. Clinical Studies on Relationship of Pyelonephritis to Hypertension
Hans G. Grieble, University of Illinois, Chicago, Illinois

9:10 Morphologic Studies on Relationship of Pyelonephritis to Hypertension
Sheldon C. Sommers, Massachusetts Memorial Hospitals, Boston, Mass.

9:20 Mechanisms of Nephrogenic Hypertension
Irvine H. Page, Cleveland Clinic, Cleveland, Ohio

9:40 General Discussion

10:00 Intermission

10:15 Inborn Errors of Tubular Dysfunction
C. E. Dent, University College Hospital Medical School, London, Eng.

10:35 A.M. Mucosubstances in the Urine
William H. Boyce, Wake Forest College, Winston-Salem, N. C.

10:55 Renal Mechanisms and Hematopoiesis
Leon O. Jacobson, University of Chicago, Chicago, Illinois

11:05 Relationship of Potassium Depleted Kidney to Pyelonephritis
Robert C. Muehrcke, Presbyterian — St. Luke's Hospital, Chicago, Ill.

11:15 General Discussion

11:50 Summation
Maurice B. Strauss, Veterans Administration Hospital, Boston, Mass.

12:30 Luncheon

Third Afternoon Session — Saturday, October 9, 1959

TREATMENT OF PYELONEPHRITIS

Chairman: *Maxwell Finland,* Harvard Medical School, Boston

2:00 P.M. Antibiotics as Inhitors of Bacterial Cell Wall Synthesis
Jack L. Strominger, Washington University, St. Louis, Missouri

2:30 Restrictions Imposed by Renal Failure on the Use of Antibiotics in Patients with Pyelonephritis
Calvin M. Kunin, Thorndike Memorial Laboratory, Boston, Mass.

2:45 Patterns of Antibiotic Absorption and Excretion
James M. Colville, Henry Ford Hospital, Detroit, Michigan

2:55 Renal Toxicity of Chemotherapeutic Agents
Charles R. Kleeman, Veterans Administration Center, Los Angeles, California.

3:05 Intermission

3:10 Therapy of Experimental Pyelonephritis
Myron W. Fisher, Research Laboratories, Parke, Davis & Co:, Detroit, Michigan

3:20 Long-Term Therapy of Pyelonephritis
Edward H. Kass, Harvard Medical School, Boston, Massachusetts

3:40 The Present Status of Chemotherapy of Pyelonephritis
Maxwell Finland, Harvard Medical School, Boston, Massachusetts

4:00 General Discussion

4:25 Summation of Symposium
Edward H. Kass, Harvard Medical School, Boston, Massachusetts

ABSTRACTS OF RECENT PUBLICATIONS OF THE PROFESSIONAL STAFF OF THE HENRY FORD HOSPITAL AND THE EDSEL B. FORD INSTITUTE FOR MEDICAL RESEARCH

COLOSTOMY CLOSURE BY THE INTRAPERITONEAL METHOD. J. BARRON, AND L. S. FALLIS. Dis. Colon & Rectum 1:466, 1958.

A series of 200 patients in whom colostomy stomas have been closed by the intraperitoneal method is presented. There were no deaths. There was only one anastomotic failure. Morbidity is insignificant. The intraperitoneal method of colostomy closure is preferable to the extraperitoneal procedure which subjects the patient to the discomfort of repeated application to the spur, of the crushing clamp and fails to accomplish its purpose in a high percentage of cases.

*LIVER CHOLESTEROL MOBILIZATION IN MICE AS EFFECTED BY DIETARY BETA-SITOSTEROL AND CHOLIC ACID. W. T. BEHER AND W. L. ANTHONY. Proc. Soc. Exper. Biol. & Med. 99:356, 1958.

In a previous study on mobilization rate of accumulated plasma cholesterol in the rabbit, β-sitosterol had a slight, initial accelerating effect. Alfin-Slater *et al.* have reported that soybean sterols, composed mainly of β-sitosterol and stigmasterol, have little effect in preventing blood cholesterol accumulation but have considerable effect in reducing cholesterol deposition in liver. Therefore, it was of interest to study the effect of β-sitosterol on rate of mobilization of accumulated liver cholesterol. Recent reports on cholesterol metabolism have shown that bile acids are important agents affecting cholesterol mobilization. Our studies have demonstrated that cholic acid blocks liver cholesterol mobilization in mice. Since cholic acid apparently alters the pathway of cholesterol metabolism, it seemed worthwhile to investigate the effect of β-sitosterol on mobilization of accumulated liver cholesterol in animals fed cholic acid. Cholic acid prevents mobilization of elevated liver cholesterol. β-sitosterol did not increase rate of mobilization of accumulated mouse liver cholesterol. β-sitosterol reduces in large measure the effect of cholic acid on liver cholesterol mobilization.

STENOSIS OF THE SPHINCTER OF ODDI AS A CAUSE OF JAUNDICE. A. BLOCK, B. E. BRUSH, L. PONKA AND A. CREPEAU. A.M.A. Arch. Surg. 76:888, 1958.

Stenosis of the sphincter of Oddi is a rare cause of obstructive jaundice in the absence of other abnormalities of the biliary tract. Surgical correction of isolated stenosis of the sphincter of Oddi will relieve obstructive jaundice, providing evidence of the clinical importance of this lesion. A mild to moderate degree of induration

*From Edsel B. Ford Institute for Medical Research.

in the head of the pancreas frequently is an associated abnormality in obstructive jaundice due to stenosis of the sphincter of Oddi. Stenosis of the sphincter of Oddi is more frequently present in association with biliary tract lithiasis or pancreatitis in the absence of jaundice. In our experience dilatation of the sphincter of Oddi is not followed by the production or recurrence of stenosis. If stenosis of the sphincter of Oddi is pronounced, transduodenal sphincterotomy should be performed. Before the diagnosis of sphincter of Oddi is made, the presence of an impacted stone or malignancy must be ruled out and the presence of definite narrowing of the lumen of the sphincter demonstrated. Results of surgical correction of stenosis of the sphincter of Oddi are good. An evaluation of the sphincter of Oddi should be a routine part of every commonduct exploration.

LOCAL OR GENERAL ANESTHESIA FOR ESOPHAGOSCOPY, LARYNGOSCOPY AND BRONCHOSCOPY; AN EVALUATION OF 300 CASES. D. S. Bolstad and J. W. Ditzler. Ann. Otol. Rhin. & Laryngol. 67:1154, 1958.

Three hundred and twenty-five administrations of Hydroxydione are reviewed. Ninety per cent of these patients were submitted to suspension laryngoscopy, adult tonsillectomy, bronchoscopy, esophagoscopy and other procedures about the airway. Viadril, or Hydroxydione, a non-functioning steroid, is a profound sedative, lacking in analgesia but possessed of excellent jaw relaxing qualities exacting a minimal price on respiration. When coupled with topical or local ansthesia and use of narcotic drugs in small doses, it is a superior method for ear, nose and throat anesthesia in the adult from the standpoint of the patient, anesthetist and surgeon. Slowness in onset and recovery, vein irritation and the frequent satisfactory usage of solely local anesthesia restricts this drug to procedures where topical or local alone appears to be inadequate.

PLASMA PROTEINS IN MALIGNANT DISEASE. M. J. Brennan, W. L. Simpson and G. Betanzos. Postgrad. Med. 24:36, 1958.

The abnormalities of serum enzyme activities and of serum protein distribution generally indicate deterioration in patients with cancer. Reversal of these abnormalities accompanies remission of the malignant disease. These various indexes may provide a more reliable measure of therapeutic response than the patient's subjective impression, and they may be employed when inaccessible tumor growth makes direct measurement of response impossible. The continued study of blood proteins from patients with cancer may contribute not only to practical diagnosis and management but also to a better understanding of resulting pathophysiology, thereby pointing to more promising means of successful intervention. To date, no serum protein change has been found diagnostic of neoplastic disease.

THE TREATMENT OF POSTMASTECTOMY LYMPHEDEMA. B. E. BRUSH, J. H. WYLIE, J. BENINSON, M. A. BLOCK AND T. J. HELDT. A.M.A. Arch. Surg. 77:561, 1958.

Edema of the arm may be successfully treated by means of an appliance to reduce the swelling, plus the use of a custom-fitted sleeve when the pump is not in use or no longer needed. The pain, discomfort, and swelling are relieved. The incidence of chills, fever, and localized infection is greatly diminished. Strict adherence to instructions is important, and medical supervision of the device is imperative. Swollen arm, a troublesome sequela of radical breast surgery, need not be tolerated.

THE UNRELIABILITY OF CASUAL BLOOD PRESSURES AS AN INDEX TO CARDIOVASCULAR-RENAL DISEASE. J. R. CALDWELL AND F. W. HOLLINGER. Postgrad. Med. 24:26, 1958.

The casual measurement of blood pressure in the office is insufficient. Basal blood pressure determination, as here described, is simple and practical. Though far from ideal it is usually lower and more significant than the casual readings. In 30 minutes the physician can often obtain information which otherwise may take three or four days to obtain with the patient at rest in the hospital. Casual readings are of value in separating patients with suspected hypertension from patients with normal blood pressures. However, the basal determination is of value before prescribing antihypertensive drugs or making prognostic statements about hypertension, a diagnosis often unjustly made from casual blood pressure determinations which, in reality, are not casual.

A DIFFERENT CONCEPT OF PROTHROMBIN TIME CONTROL FOR ANTICOAGULATIVE THERAPY. M. J. CALDWELL AND E. M. PRIEST. Am. Heart J. 56:737, 1958.

Three different thromboplastins were used in the Quick one-stage prothrombin time on plasmas of patients to whom oral anticoagulants had been administered. Thromboplastin #1 gave very uniform results. Thromboplastin #2 gave shorter prothrombin times, and thromboplastin #3 gave more prolonged values and separated out a few plasmas which appeared to be different from the others.

STUDIES OF TIME-DOSE RELATIONSHIPS: THE EFFECT OF FRACTIONATION. L. A. DUSAULT, W. R. EYLER AND W. M. BURNS. Radiology 71:709, 1958.

Spontaneous mammary adenocarcinomas in C3H mice irradiated at the rate of 2,000 r/week were found to show greater response when treated three times a week than when treated on five successive days. This is true at both the 6,000 r and 8,000 r

total dose level. Normal tissue reactions were only slightly increased. An increased differential effect in tumor and normal tissue, therefore, can be obtained by this timing of treatments. The optimum interval between treatment depends on the size of the individual dose, since no difference was found between the two fractionation technics when the rate of irradiation was 2,500 r/week. The highest dosage group showed poorer results and greatly increased systemic effects. This suggests the possibility that supralethal effect may be related to impairment of host resistance.

OXYGEN THERAPY. E. O. COATES, JR., G. L. BRINKMAN, P. R. DUMKE AND E. W. GREEN. Postgrad. Med. 24:60, 1958.

Regarding the accuracy of clinical signs of hypoxia, dyspnea and cyanosis are relatively unreliable indications of lack of oxygen. Increasing pulse rate, restlessness, anxiety and an altered mental state are the most significant indications. Oxygen therapy in high concentration is often useful in conditions in which severe localized tissue anoxia exists, such as surgical shock and severe myocardial or cerebral infarction, for the primary purpose of increasing the oxygen dissolved in the plasma. We believe that administration of prolonged low-flow oxygen is beneficial in certain cases of chronic hypoxia, because of its effect in lowering pulmonary hypertension and because it helps to restore cardiac and pulmonary compensation. A special nasal catheter is employed for the administration of this oxygen. Possible harm from the use of oxygen was emphasized because of its tendency to induce further hypoventilation and carbon dioxide retention in certain patients with chronic hypoxia. The accompanying syndrome of so-called carbon dioxide narcosis is fortunately uncommon, but recognition is important since it is usually reversible. A second possible harmful effect is that of toxicity from the oxygen itself as a result of its prolonged use in a concentration of 100 per cent. Experimental and clinical observations indicate that such exposure may produce an irritant broncho-pneumonia, but that this occurs clinically only under very unusual circumstances. Of the various technics of oxygen administration which have been discussed, the nasal catheter is the method favored for most purposes because of its ease and availability, the good concentration of oxygen obtained, and the absence of carbon dioxide accumulation in the inspired air.

PHOSPHATE DIABETES; A CASE STUDY OF OSTEOMALACIA. B. FRAME AND R. W. SMITH, JR. Am. J. Med. 25:771, 1958.

A case report is presented of a patient with vitamin D-resistant osteomalacia. The basic defect was considered to be a reduced renal tubular reabsorption of phosphorus with resulting hypophosphatemia. After lengthy therapy with calcium lactate and large doses of vitamin D was only partially successful, supplemental phosphorus administered orally resulted in marked improvement. Symptoms abated,

calcium and phosphorus retention increased, and reossification was noted in x-ray films of the demineralized skeleton. Parathyroidectomy was performed but its contribution to the over-all results cannot be stated.

PREPARATION OF THIN UNDECALCIFIED BONE SECTIONS BY RAPID MANUAL METHOD. H. M. Frost. Stain Technol. 33:273, 1958.

Sections from 3 μ to over 100 μ thick of fresh, unfixed, unembedded, undecalcified and undehydrated bone are made by grinding 1 to 2 mm slabs of the desired orientation on waterproof carborundum abrasive paper, grit No. 320, 360 or 400. The manner of controlling the section is the crux of the technique. The section is held by wrapping a fresh strip of sandpaper around a 3" x 1" slide and accomplishing the grinding on a used piece of paper. The abrasive points on the fresh paper effectively prevent the section from sliding off the side. The specimen is kept wet with water during the entire procedure. Sections are then stained, and excess surface stain can be ground off in similar fashion. After washing in dilute detergent solution to remove adherent debris, the section is air dried and mounted in any nonacidifying resinous media. The method is suitable for wood and for fruit pits also.

DIABETIC ACIDOSIS. H. L. Green and F. W. Whitehouse. J. Michigan M. Soc. 57:1410, 1958.

Patients with diabetic acidosis are critically ill. The diagnosis must be quickly established and treatment initiated. Management should be energetic, and the patient must be carefully followed until he is out of danger. Many complications can occur with or from acidosis, and it is best prevented by rational and careful management of the diabetic patient.

URETHROCYSTOGRAMS; METALLIC BEAD CHAIN TECHNIQUE. C. P. Hodgkinson, H. P. Doub and W. T. Kelly. Clin. Obst. & Gynec. 1:668, 1958.

More precise indications than a simple history of involuntary loss of urine on sudden exertion and the finding of a cystocele, are necessary in patients suffering from stress incontinence to answer such questions as, what is the basic pathology? Is it neurogenic or anatomic? Why did the previous operative procedure fail? Is conservative or operative treatment now necessary and, if operative treatment is now necessary, which procedure should be selected, and why? Diagnostic knowledge is incomplete and unequivocal answers cannot be given. Routine urologic and gynecologic studies will generally serve to rule out such conditions as bladder calculi, fistula, "false" incontinence of extreme urgency, and chronic infection of the urinary tract. The purely functional, neurogenic, and anatomic causes must be studied by special

methods. The metallic bead chain technique in roentgen study of urethrovesical relationships has value as a diagnostic aid for the study of the anatomic changes in the etiology of urinary stress incontinence, and is described in detail.

URETHROVESICOPUBIC RELATIONSHIPS AND URINARY STRESS INCONTINENCE. IV. THE UTERINE SUSPENSION SYNDROME. C. P. HODGKINSON AND W. T. KELLY. Am. J. Obst. & Gynec. 76:1114, 1958.

Two groups of patients have been presented whose urethrocystopubic relationships showed anterior displacement of the bladder, reduction in the size of the posterior bladder segment, and evidence of posterosuperior extravesical pressure. Urinary frequency, urgency, and stress incontinence were the associated subjective complaints. It appeared probable that these anatomic changes played no more than ancillary roles in the etiology of urinary stress incontinence. Yet, unless they were corrected, successful establishment of urinary control was in jeopardy. Moreover, because of these peculiar urethrovesicopubic relationships, the surgical treatment must be carefully contemplated. Vaginal plastic operations are least likely to be successful. Abdominal procedures which involve hysterolysis and retropubic urethropexy are best. Because the anatomic relationships are opposite to those usually observed in urinary stress incontinence, because they cannot be properly evaluated by clinical means alone, and because combined operative procedures must be employed if success is to be obtained, it has been found convenient to designate these objective signs and subjective symptoms, when occurring concomitantly, as the uterine suspension syndrome.

EFFECT OF ADMINISTRATION OF PHENINDIONE ON BLOOD LEVELS OF PROTHROMBIN, AUTOPROTHROMBIN I AND AUTOPROTHROMBIN II. S. A. JOHNSON, M. J. CALDWELL AND E. M. PRIEST. J. Appl. Physiol. 13:411, 1958.

Phenindione was administered to 14 patients in the Cardiology Division. Prothrombin, autoprothrombin I and autoprothrombin II determinations were carried out on plasma and serum samples drawn before administration of the drug, during and following administration. The prothrombin, autoprothrombin I and II all fell in concentration simultaneously. Prothrombin and autoprothrombin I recovered at the same rate, while autoprothrombin II returned to the original concentration much later. The response of the three components to administration of vitamin K_1 was also observed.

RELATIONSHIP OF PLATELET FACTOR 1 AND PLATELET FIBRINOGEN TO PLASMA. S. A. JOHNSON, R. W. MONTO AND M. J. CALDWELL. J. Appl. Physiol. 13:406, 1958.

Some platelet factors appear, in the light of our present knowledge, to be

characterized by activities similar to those in plasma. These platelet activities may be simply 'artifacts,' or a useful and necessary function in the blood coagulation mechanisms may be served by having the activity reside in both plasma and platelets. Two such activities are platelet factor I (accelerator) and platelet fibrinogen or clottable factor. The role of platelet factor I is somewhat clarified by the fact that a normal prothrombin consumption time was found in the absence of plasma Ac-globulin and platelet factor I. These same platelets which lacked platelet factor I were able to pick up Ac-globulin from normal plasma. In another case, the concentration of platelet fibrinogen appeared to be independent of the concentration of plasma fibrinogen, suggesting that these two types of fibrinogen may have some significant difference.

INDUCED CARDIAC ARREST IN OPEN HEART SURGICAL PROCEDURES. C. R. LAM, T. GAHAGAN, C. SERGEANT AND C. MOTA. Bull. Soc. Internat. Chir. 17:26, 1958.

After we had adopted the drug acetylcholine as the agent for inducing cardiac arrest, our attention was drawn to the experimental work of Melrose of London. He recommended that the heart be stopped by the intracoronary injection of heparinized blood containing potassium citrate. Because we had discontinued the use of potassium chloride for the reasons outlined above, we were not inclined to try the Melrose technic clinically. We did a few experiments in the laboratory to compare the two methods. The periods of resuscitation were slightly longer with the potassium citrate and there was one instance of intractable ventricular fibrillation.

IS AORTIC STENOSIS CURABLE? C. R. LAM. Postgrad. Med. 24:11, 1958.

There are several feasible operations for the relief of aortic stenosis, but the most practical ones are (1) the transventricular dilating procedure for acquired stenosis, and (2) open aortotomy under moderate hypothermia for congenital stenosis. The latter method will probably be applied to more and more cases of acquired disease. Aortic stenosis may not be a curable lesion as far as restoring a completely normal anatomic situation is concerned, but many patients can be improved if there are not too many complicating lesions and if the type of operation is carefully selected.

CLINICAL PATHOLOGICAL CONFERENCE IN A HOSPITAL IN U. S. A., WITH DISCUSSION OF A CASE OF SICKLE CELL ANEMIA. G. LAUBINGER. München. Med. Wchnschr. 100:842, 1958.

Postgraduate instruction, modulated through conferences, is common practice in the teaching hospital in the U. S. A., but is not conducted in this manner in Germany. The purpose, organization and extent of these conferences is discussed

and the protocol is given of a CPC, which probably represents a most valuable teaching exercise. The clinical discussant was Dr. Brinkman, while Dr. Horn discussed the pathological findings.

The patient was a 72 year old negress, who was suffering from arteriosclerotic hypertensive heart disease and who also had sickle cell trait. This latter became symptomatic on air travel but pertinent only after she finally reached a stage of cardiac insufficiency with hypoxia, causing thrombi of sickle cells with pulmonary and cerebral infarctions. An outstanding finding in this case were bone marrow infarctions, which are usually seen in pure sickle cell disease only and not in sickle cell trait.

NEPHROGENIC HYPERTENSION (GOLDBLATT KIDNEY) FOLLOWING OPERATIVE TRAUMA TO THE RENAL ARTERY. R. T. McDonald, D. E. Szilagyi and R. F. Smith. Circulation 18:71, 1958.

A report is given of an instance of malignant arterial hypertension supervening on inadvertent surgical trauma and eventual thrombosis of the right renal artery, and cured by right nephrectomy. The sequence of clinical events, the pathologic findings, and the bioassay of the parenchyma of the removed kidney are interpreted as proofs that the hypertension in this case was a clinical counterpart of the experimental hypertension produced under certain conditions by the constriction or occlusion of the renal artery.

PROGRESSIVE EXOPHTHALMOS DEVELOPING 12 YEARS AFTER THYROIDECTOMY FOR DIFFUSE TOXIC GOITER. J. J. McHugh and R. C. Mellinger. Ann. Int. Med. 49:955, 1958.

The development of severe infiltrative ophthalmopathy and localized pretibial myxedema 12 years after subtotal resection of a toxic diffuse goiter suggests that the physiologic disturbance of Graves' disease had either persisted or recurred. However, the patient was euthyroid and responded to the administration of thyroxine with a normal decrease in thyroid function, demonstrating an intact pituitary-thyroid relationship. This evidence is interpreted to indicate that the exophthalmos-producing factor is not thyrotropin, and is independent of both thyrotropin and thyroid hormone levels.

CONGENITAL DISORDERS OF THE GONADS. R. C. Mellinger. Postgrad. Med. 24:43, 1958.

Three groups comprise the known congenital gonadal anomalies: gonadal dysgenesis, adrenal virilism and hereditary male pseudohermaphroditism due to maternal antitesticular factors. Individual patients can be classified only by determination of

their sex in several different spheres: genetic, by chromosomal study; gonadal, by histologic study; somatic, by anatomic study; and endocrine, by hormonal study. Anomalous sexual development should be considered an imbalance of the normal male-female relationship. Anatomically, endocrinologically and psychologically, the human being is normally intersexual. Only in the sphere of the chromosome is a person all male or all female; this finding may prove ultimately to be more a delusion than a fact as more refined analysis of sex chromatin is obtained. At present we do not recognize abnormalities of the sex chromatin, but at all subsequent levels of development — the differentiation of the fetal gonad, the development of the genital ducts, the secretion of the sex hormones, or the orientation of the psychologic sex drive — imbalance of the normal male to female ratio may occur, resulting in clinical sexual anomalies.

*STRUCTURE OF SCHMIDT'S ALUMINUM HYDROXIDE GEL. P. S. SANTOS, A. VALLEJO-FREIRE, J. PARSONS AND J. H. L. WATSON. Experientia 14:318, 1958.

These results show that the particles which constitute the solid phase of Schmidt's gels are different from those of the Willstätter's C-gamma gels, but are similar to those of the C-beta gels, which are also composed of fibrils, having a Boehmite structure, shown in a previous paper, formed by condensation polymerization of the amorphous aluminum hydroxide molecules of the C-alpha gel. Their X-ray diffraction data do not coincide exactly with the data of well crystallized Boehmite because the fibrils are exceedingly small and friable and are neither completely polymerized nor oriented. After autoclaving, Schmidt's gels do not change spontaneously into Bayerite and Gibbsite which constitute the C-gamma gels, and from this point of view they are different from the C-beta gel. This stability of crystalline structure, of particle size, and of shape in Schmidt's gels make them superior to Willstätter's C-beta or C-gamma gels for preparation of adsorbent. In addition to the ammonium alum, other aluminum salts, like the chloride, the nitrate, or the acetate, can be used for preparing gels composed of Boehmite fibrils, but the fibrils in these are thicker in diameter and have therefore a smaller surface area than those from Schmidt's gel.

DETERMINATION OF SEX BY SEX CHROMOSOMES. J. P. PRATT. Clin. Obst. & Gynec. 1:686, 1958.

Genetic sex is established at the time of fertilization of the ovum. The gonadal sex, secondary sex characteristics, the mental and emotional sex may or may not conform to the genetic sex. Determination of sex by the chromatin pattern refers only to the genetic sex. When a discrepancy of sex manifestations is discovered, determination of the genetic sex is a valuable aid to the interpretation of the discrepancy.

*From Edsel B. Ford Institute for Medical Research.

This new field of study is fascinating, but the present discussion is limited to the methods of determining the genetic sex.

Study of the nuclear morphology of the neural cells of the cat has led to the discovery of a chromatin pattern in the tissues of the female which differs from that in the male. The sex-specific chromatin pattern in neural cells was soon found to exist in all the tissues of the body of other mammals including man. The intermitotic nuclei of females contain a mass of sex chromatin that is characteristically planoconvex in shape and is situated adjacent to the inner surface of the nuclear membrane. The chromatin mass may be found in about three fourths of the female nuclei, but the nuclei of males seldom contain a similar mass. These chromatin masses are illustrated in skin from a normal woman and in leucocytes.

SERUM TRANSAMINASE AND SERUM IRON IN LIVER DISEASE. J. A. RINALDO AND D. G. REMP. Postgrad. Med. 24:48, 1958.

A serum transaminase value greater than 250 units by the method employed in the present study was strong evidence that hepatitis was present, while a level greater than 300 units was almost diagnostic. If SGO-T and conventional liver tests are equivocal, serum iron concentration should be determined. This is feasible, since serum iron levels generally remain elevated longer than those of serum transaminase. Serum iron values greater than 180 μg. are suggestive of hepatitis, and those greater than 200 are diagnostic of hepatitis when hemolytic anemia and hemochromatosis have been excluded. An increased transaminase level is more effective than increased iron concentration for determining the presence of hepatitis. Analysis of iron levels adds to the effectiveness of conventional liver tests in making this diagnosis. Determination of serum iron concentration is technically easier than that of serum transaminase. In a laboratory in which transaminase analyses cannot be performed, it may be possible to utilize the serum iron test.

WHIPPLE'S DISEASE — OBSERVATION ON SYSTEMIC INVOLVEMENT. I. CYTOLOGIC OBSERVATIONS. J. C. SIERACKI. A.M.A. Arch. Path. 66:464, 1958.

Study of the tissues of patients with Whipple's disease has shown a widespread involvement with cells containing a characteristic cytoplasmic particle. The presence of these cells in the peripheral lymph nodes allows the diagnosis to be made during life without recourse to laparotomy. Cytologic studies of the material from seven cases of Whipple's disease demonstrated a characteristic periodic acid-Schiff (P. A. S.)-positive cytoplasmic particle in affected cells in all cases. The cells containing these sickle-form particles are described in some detail.

CONGENITAL FUSION OF THREE LUMBAR VERTEBRAL BODIES. S. STANISAVLJEVIC AND E. G. ST. JOHN. Radiology 71:425, 1958.

A single case of congenital fusion of three lumbar vertebral bodies has been presented. An associated anomaly was hypoplasia of the eighth thoracic vertebra, with congenital fusion of two ribs on the right at this level.

THE APPLICABILITY OF ANGIOPLASTIC PROCEDURES IN CORONARY ATHEROSCLEROSIS: AN ESTIMATE THROUGH POSTMORTEM INJECTION STUDIES. D. E. SZILAGYI, R. T. MCDONALD AND L. C. FRANCE. Ann. Surg. 148:447, 1958.

In an inquiry into the feasibility of applying direct surgical technics to the correction of the occlusive process in coronary atherosclerosis, the distribution and state of advancement of the atherosclerotic lesions were studied in 190 hearts after injection with a barium-glycerine mixture at autopsy. Seventy-six of these specimens (all from cases without clinical arteriosclerotic heart disease) showed no occlusive changes of importance. Among the 114 hearts with occlusive lesions, 35 came from patients with no clinical manifestation of coronary atherosclerosis; 79 of the specimens were obtained in cases with clinical atherosclerotic heart disease of which 23 had had angina pectoris as their sole or main clinical manifestation.

The earliest and most sharply localized occlusive lesions were found in the subclinical group; the most advanced and widespread involvement occurred in the clinical group with angina. In general, it appeared that coronary atherosclerosis when clinically manifest tends to be generalized. Judged by technical criteria which take into consideration the topographic accessibility, luminal size and outflow characteristics of the main coronary branches, 43 per cent of the hearts in the *subclinical* groups were judged inoperable; 17 per cent of the hearts in the same group were regarded as capable of palliation and 40 per cent as capable of cure by direct surgical means. In the *clinical* group the theoretical rate of inoperability was found to be 44 per cent and the rate of curability 13 per cent. The importance of a safe and reliable clinical method of coronary angiography for the realization of the potentialities of angioplastic procedures in the treatment of these lesions was emphasized.

THE CLINICAL USE OF AN ELASTIC DACRON PROSTHESIS. D. E. SZILAGYI, L. C. FRANCE, R. F. SMITH AND J. G. WHITCOMB. A.M.A. Arch. Surg. 77:538, 1958.

An arterial substitute with elastic qualities is described. Woven of plain Dacron yarn in the woof and elasticized (Helanca) Dacron yarn in the warp as straight tubes and bifurcations, the prosthesis is seamless, smooth-walled, finely porous, light and soft, and has the ability to elongate. It is easy to procure, store, and sterilize. In

animal experiments using long aortic bypass implants, during 11 months of observation, the elastic Dacron prosthesis showed an excellent rate of patency, even when traversing a tortuous course; arteriogenesis around the implants was good and tissue reactivity low. During nine months of implantation the initial tensile strength of the prostheses was essentially unchanged. In spite of unfavorable criteria of case selection, during nine months of experience, in 43 clinical cases, the prosthesis yielded a patency rate only slightly below that obtained by us with homografts. The assumption that the *late* patency rate of these prostheses will be better than that of homografts is supported both by theoretical considerations and by experimental evidence, but it will not be proved or disproved until the results will have been followed for much longer periods of time.

EXPERIMENTAL AND CLINICAL UTILIZATION OF A PROSTHESIS FOR REPLACEMENT OF THE TRACHEA. R. E. Taber and L. Tomatis. A.M.A. Arch. Surg. 77:576, 1958.

Only infrequently will the surgeon be called upon to replace extensive tubular segments of the trachea. When the extent of the resection exceeds four to five tracheal rings in length, the need for prosthetic reconstruction arises. Previously reported tracheal substitutes which have received clinical trial consisted of nonporous metallic and plastic tubes or wire mesh covered with autogenous tissue, such as fascia or dermis. The postoperative problems involved with the use of most of these have usually occurred late in this period. These difficulties were secondary to loss of prosthesis fixation, with resulting tracheostenosis due to contraction of the tracheal ends or migration of the tubular foreign body within the tracheal lumen. It would appear that one solution of this complication is the use of a prosthesis fixation method which is ultimately dependent upon infiltration by host tissues, resulting in incorporation of the tracheal substitute into the remaining airway as a permanent structure. Clinical utilization of this tracheal substitute has been made in the emergency management of a 37-year-old patient in whom it was necessary to replace the entire thoracic trachea which was involved by reticulum-cell sarcoma. A satisfactory airway resulted, until the patient died on the 22d postoperative day of hemorrhage due to erosion of the innominate artery by neoplasm.